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Pharmacological fMRI on the effects of Fluoxetine on functions of Working Memory, Impulsiveness and Cognitive Flexibility in boys with Attention Deficit Hyperactivity Disorder and boys with Autism Spectrum Disorder

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Pharmacological fMRI on the effects of Fluoxetine on functions of Working Memory, Impulsiveness and Cognitive Flexibility in boys with Attention Deficit Hyperactivity Disorder and boys with Autism Spectrum Disorder

Kaylita Charlene Chantiluke

Thesis submitted to the University of London for the Degree, Doctor of Philosophy

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are highly comorbid and share deficits in working memory, motor inhibition and cognitive flexibility. Serotonin modulates these functions and Fluoxetine has positive clinical effects in these disorders.

Functional magnetic resonance imaging was used to scan 22 ADHD and 22 ASD boys, under placebo or an acute dose of Fluoxetine, in a double-blind, placebo-controlled, randomised design, while they performed N-Back, Stop and reversal learning tasks. Repeated measures analyses within patients assessed drug effects. Patients under each drug condition were compared to 20 controls to test for normalisation effects.

During the N-Back, under placebo, relative to controls, ADHD and ASD groups shared underactivation in right dorsolateral prefrontal cortex (DLPFC). ASD boys showed disorder-specific deactivation of posterior cingulate (PCC). Under Fluoxetine, DLPFC underactivation in ASD was significantly normalised and PCC deactivation was increased in ADHD, relative to controls.

During the Stop task, under placebo, relative to controls, ASD boys showed disorder-specific overactivation in bilateral inferior frontal cortex while ADHD boys showed disorder-specific underactivation in ventrolateral prefrontal cortex. Under Fluoxetine, prefrontal dysfunctions were significantly normalised in both disorders, due to inverse up and downregulation effects of Fluoxetine in these regions, in each disorder.

During reversal learning, under placebo, ASD boys exhibited disorder-specific underactivation in medial prefrontal cortex (mPFC), compared to controls and ADHD, while patients shared decreased activation in precuneus. Under Fluoxetine, mPFC activation was upregulated and normalised in ASD boys, but down-regulated in ADHD boys.

Fluoxetine had disorder-dissociated, inverse effects on frontal brain function in ADHD and ASD during inhibition and reversal learning. During working memory Fluoxetine improved task-positive frontal activation in ASD and task-negative activation in ADHD. These inverse effects of Fluoxetine on frontal brain activation in the two disorders potentially reflect inverse baseline serotonin levels and may underlie its clinical effect.

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List of Abbreviations

ADI: Autism Diagnostic Interview

ADOS: Autism Diagnostic Observation Schedule

SDQ: Strengths and Difficulties Questionnaire

SCQ: Social Communication Questionnaire

CPRS: Conners' Parent Rating Scale

SSRT: Stop Signal Reaction Time

WCST: Wisconsin Card Sorting Task

ID/ED: Intra-Dimensional/Extra-Dimensional

WM: Working Memory

ToM: Theory of Mind

ROI: Region of Interest

mPFC: Medial Prefrontal Cortex

vmPFC: Ventromedial Prefrontal Cortex

dmPFC: Dorsomedial Prefrontal Cortex

OFC: Orbitofrontal Cortex

IFC: Inferior Frontal Cortex

VLPFC: Ventrolateral Prefrontal Cortex

DLPFC: Dorsolateral Prefrontal Cortex

SMA: Supplementary Motor Area

ACC: Anterior Cingulate Cortex

PCC: Posterior Cingulate Cortex

DMN: Default Mode Network

5-HT: Serotonin

MPH: Methylphenidate

MAO: Monoamine Oxidase

DRN: Dorsal Raphe Nucleus

MRN: Median Raphe Nucleus

SERT – Serotonin Reuptake Transporter

SSRI: Selective Serotonin Reuptake Inhibitor

SNRI: Serotonin and Noradrenaline Reuptake Inhibitor

ATD: Acute Tryptophan Depletion

ATL: – Acute Tryptophan Loading

5-HTTLPR – Serotonin Transporter Long Polymorphic Repeat Region

Chapter 1 – Executive Dysfunction in ADHD and ASD

1.1 – Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders – IV (DSM-IV) (American et al., 1994), Attention Deficit Hyperactive Disorder (ADHD) is a neurodevelopmental disorder defined by levels of inattention, impulsivity and hyperactivity which are inappropriate for the age of the individual (American et al., 1994). In order for a clinical diagnosis to be made, a team of clinicians will conduct a semi-structured interview with the primary care-giver of the child and, depending on his or her age, the child, to ascertain whether the symptoms of inattention, impulsivity and hyperactivity have been present before the age of seven, have persisted for a number of years, and significantly impair home life, social life and school/work life (American et al., 1994). School observations, as well as interviews and reports from teachers, are used in conjunction with the information from the parent in order to obtain a holistic view of the child's behaviour. Clinicians use scores on two different domains focusing on inattention and hyperactivity/impulsivity to decide whether the individual has predominantly hyperactive/impulsive, inattentive or combined symptoms of ADHD and these three groupings are known as the three subtypes of ADHD (American et al., 1994). ADHD has a gender ratio of 3:1 and a current prevalence of 3-8% (American et al., 1994, Polanczyk et al., 2007, Ramtekkar et al., 2010). It is one of the most frequently diagnosed childhood disorders and often persists into adulthood, with recent research reporting persistence levels of 66-78% (Barkley et al., 1992, Biederman et al., 2010). It is a debilitating disorder, associated with poor academic performance, increased risk taking, addictive behaviours and increased levels of crime (Biederman et al., 2004, Ohlmeier et al., 2008, Fletcher and Wolfe, 2009). It is also highly comorbid with externalising behavioural disorders such as Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) ((Jensen et al., 1997, Willcutt et al., 1999, Connor and Doerfler, 2008).

Another neurodevelopmental disorder, which may initially appear very different from ADHD, is Autism Spectrum Disorder (ASD). ASD is an umbrella term for a group of neurodevelopmental disorders which all have impairments in communication

and social interaction, and the presence of restricted and repetitive, otherwise known as stereotyped, behaviours (American et al., 1994). These three components which are vital for ASD diagnosis are often called ‘the ASD triad’ and all three must be present for an ASD diagnosis to be made. The triad start to become evident between the ages of 3-5 when children begin to talk and interact with their peers, but they are often present from the first year of life. Two of the most widely used diagnostic instruments for ASD are the Autism Diagnostic Interview – Revised (ADI) and the Autism Diagnostic Observation Schedule (ADOS). The ADI is a detailed interview with the primary care giver of the individual which assesses symptoms of the triad and their current and past prevalence (Lord et al., 1994). The ADOS is a selection of tasks that are performed with the individual to assess their current autistic characteristics based on the triad and the tasks vary dependent on the verbal ability of the person undergoing the ADOS (Lord et al., 2000). Much like ADHD, ASD has a higher prevalence in boys than girls with a gender ratio of 4.3:1 (Rivet and Matson, 2011). The global prevalence of ASD is 20 in 10,000 (Williams et al., 2006c) and the disorder has a high rate of persistence into adulthood, with recent research reporting levels of up to 58% (Howlin et al., 2004).

ADHD and ASD share many behavioural characteristics; it has been consistently reported that children with ASD have clinically significant levels of hyperactivity and inattention, with up to 30% meeting the clinical criteria for ADHD (Goldstein and Schwebach, 2004, Gadow et al., 2006, Gadow et al., 2005, Leyfer et al., 2006, de Bruin et al., 2007, Simonoff et al., 2008, Sinzig et al., 2009, Gargaro et al., 2011, St. Pourcain et al., 2011, Rommelse et al., 2011). Furthermore, it has been observed that children with ADHD also have traits of the ASD triad, namely poor social interaction (Clark et al., 1999, Reiersen et al., 2007, Mulligan et al., 2009, Kochhar et al., 2011). Several authors have also commented on the arbitrary distinctions that have been drawn between these two disorders and whether the diagnostic criteria for these conditions should be viewed together as a neurodevelopmental spectrum (Hattori et al., 2006, Funabiki et al., 2011, van der Meer et al., 2012). Currently , DSM-IV does not allow co-diagnosis of ADHD and ASD (American et al., 1994). In response to the overwhelming evidence for overlapping behaviours in these two disorders, the upcoming DSM-V will allow a co-diagnosis of both ASD and ADHD to be given (<http://www.dsm5.org>). However,

relatively little is known about the shared and disorder-specific biological abnormalities present in these two overlapping disorders. Greater knowledge on the similarities and disorder-specific differences between ADHD and ASD, particularly in a biological measure such as neurofunctional activity, has the potential to aid diagnosis and shed light on treatment targets.

However, before biological measures can be discussed, one must focus on neuropsychology, as this is the area which defined the cognitive impairments present in ADHD and ASD and suggested that brain based abnormalities may play a role in the deficits observed. Executive functions are defined as the higher processing aspects of our cognition that work together to allow goal directed behaviour to occur (Stuss and Alexander, 2000). Executive functions involve cognitive processes such as working memory (WM), inhibition, cognitive flexibility, attention, planning, temporal foresight and performance monitoring (Stuss and Alexander, 2000). Executive functions can be divided into “cool” and “hot” depending on whether they involve purely abstract or reward related tasks, respectively (Zelazo and Müller, 2002). Due to the cognitive performance deficits observed in ADHD and ASD it was hypothesised that both ADHD (Barkley, 1997, Willcutt et al., 2005) and ASD (Ozonoff et al., 1991, Pennington and Ozonoff, 1996, Corbett et al., 2009) may be disorders of executive dysfunction. Therefore, elucidating the executive function profiles of ADHD and ASD will enable one to ascertain which cognitive functions would be best to investigate at a neurofunctional level. Due to the focus of this PhD, research investigating the executive function domains of WM, inhibition and cognitive flexibility in children with ADHD and children with ASD will be reviewed in detail below. Other cognitive deficits pertaining to each of the disorders, but which are not specifically relevant for the present PhD, will be reviewed only briefly for completeness.

1.2 – Working Memory

1.2.1 – Working Memory in ADHD

WM is defined as the ability to temporarily store and manipulate information in order to guide and direct behaviour (Baddeley, 1996). There are various WM models, however, Baddeley's two component model is the most accepted and referenced due to the large amount of data which supports it (Baddeley, 2003). This model states that there are separate phonological and visuo-spatial storage components in WM which deal with verbal and visuo-spatial stimuli. These components are overseen by a central executive component which enables the manipulation of the data stored in the phonological and visuo-spatial components, as well as drawing on information from long term memory (Baddeley, 2003).

Verbal storage and central executive function are often assessed by tasks such as the digit span forward and digit span backwards, respectively. These tasks involve repeating a string of numbers in the order they were presented, the forward condition, and then in the reverse, the backward condition. After each correct trial the number of digits in the sequence increases, with the largest sequence consisting of nine digits. A closely linked paradigm known as the spatial span forward and backwards is frequently used to assess visuo-spatial storage and central executive function, however, spatial information in the form of a sequence of squares on a screen is used instead of digits. The similarities between these tasks enable easy comparison between phonological and visuo-spatial working memory abilities (Baddeley, 2003).

Another classic paradigm for measuring phonological WM is the N-Back task. In this task, a series of letters is presented to the participant one by one on the screen and the task is divided into different conditions. 0-Back requires the participant to make a response when a target letter appears, 1-Back requires a response when the letter is the same as one before it, 2-Back requires a response when the letter is the same as two before it and 3-Back requires a response when the letter is the same as three before it (Baddeley, 2003). This task is therefore parametric as it has three WM

loads of increasing difficulty. This makes the N-Back more sensitive than other WM tasks as it enables one to measure the effects of WM load on task performance.

Deficits in WM may play a role in the absentmindedness that is often reported in children with ADHD (American et al., 1994). Furthermore, there is a neuropsychological hypothesis of ADHD which posits that deficits in WM are the key impairment in the disorder and that this deficit then leads to other symptoms such as poor inhibition and hyperactivity (Stevens et al., 2002, Klingberg et al., 2005, Rapport et al., 2009, Alderson et al., 2010). Although further evidence is needed to support a link between WM deficits and ADHD symptoms, there is a large body of data which supports the presence of WM deficits in children with ADHD compared to their typically developing peers.

It has been repeatedly observed that children with ADHD, who have had a 24hr medication washout, perform worse than controls on tasks of phonological and visuospatial storage and central executive function, as is evidenced by the significantly lower scores and increased number of errors they make on both the forward and backwards component of the digit and spatial span tasks (Stevens et al., 2002, Martinussen and Tannock, 2006, Rommelse et al., 2008, Rapport et al., 2008, Kofler et al., 2010, Toplak et al., 2009, Gau and Shang, 2010, Alderson et al., 2010, Wee et al., 2010). Lower WM scores have also been reported for children with ADHD relative to controls when performing verbal and spatial free-recall tasks (Gibson et al., 2009, Crocker et al., 2011) and maze memory tasks which assess visuo-spatial memory (Wee et al., 2010). These deficits are also present in medication naïve samples, as studies using this population have also reported lower scores and increased errors using spatial span and spatial WM tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Kempton et al., 1999, Rhodes et al., 2005, Rhodes et al., 2012, Barnett et al., 2009).

When focusing on studies that have employed the N-Back task, an overall greater number of omission errors, greater intra-subject variability with increasing WM load and impaired task performance have been observed in children with ADHD compared to typically developing children (Klein et al., 2006, Pasini et al., 2007). This highlights the effectiveness of the N-Back at tapping into the phonological WM

deficits which have been consistently reported in children with ADHD (Willcutt et al., 2005, Martinussen et al., 2005, Kasper et al., 2012).

Meta-analyses investigating the full extent of the phonological and visuo-spatial WM deficit in ADHD have all supported the presence of deficits in both the storage and central executive components of both of these functions during WM tasks (Willcutt et al., 2005, Martinussen et al., 2005, Kasper et al., 2012).

Moreover, a number of studies have shown that these WM deficits have been associated with symptoms of inattention (Martinussen and Tannock, 2006) and WM training can lead to improved response inhibition, and a decrease in inattentive symptoms, in children with ADHD (Klingberg et al., 2005). This suggests that if one gains an understanding of the biological basis of the WM impairment in ADHD, and aims to normalise it, this may have an ameliorative effect on ADHD behaviour.

1.2.2 – Working Memory in ASD

Research into WM has also been conducted in children with ASD to ascertain whether they exhibit deficits in this domain, as it would provide further evidence for the executive function hypothesis of ASD and may be linked to the deficits in planning that are often reported in this patient group (Ozonoff et al., 1991, Hughes et al., 1994, Hill, 2004, Zinke et al., 2010).

Research into verbal WM has produced varied results with some studies finding deficits in the phonological loop and central executive component of WM in children and adolescents with ASD compared to their typically developing peers during forward and backward digit span, sentence span, free-recall, self-ordered pointing and N-Back tasks (Bennetto et al., 1996, Russell et al., 1996, Minshew and Goldstein, 2001, Joseph et al., 2005b, Nakahachi et al., 2006, Cui et al., 2010, Yerys et al., 2012). However, other studies have found no impairment in WM in children with ASD compared to controls during these same tasks (Ozonoff and Strayer, 2001). These conflicting findings may be due to the innate phenotypic heterogeneity of ASD, the inclusion of females and the high level of psychiatric comorbidities present in the

ASD groups. Furthermore, there is evidence in children with ASD that the parametric design of the N-Back task highlights the difficulties in phonological memory in this patient group, which may be missed in the commonly used digit and word recall tasks (Cui et al., 2010). This suggests that the N-Back may be more appropriate than other tasks for eliciting the phonological WM deficits that have been reported in ASD.

Research into visuo-spatial WM has produced more consistent results, with most studies finding a deficit in the visuo-spatial sketch pad and central executive component of WM in children with ASD compared to controls during the spatial WM and spatial span tasks of the CANTAB, oculomotor delayed response tasks and the maze memory task (Minshew and Goldstein, 2001, Minshew et al., 1999, Joseph et al., 2005a, Landa and Goldberg, 2005, Williams et al., 2005, Williams et al., 2006b, Verte et al., 2005, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010). There is, however, a small number of studies which fail to find visuo-spatial WM deficits (Griffith et al., 1999, Ozonoff and Strayer, 2001) but this may be due to the small sample sizes used in these studies, the heterogeneity of the groups and the particularly young age of the children used in Griffiths et al 1999 who were aged between 3-5 years old.

Current literature suggests that children and adolescents with ASD are impaired in WM and that this impairment is more severe in the visuo-spatial domain (Bennetto et al., 1996, Russell et al., 1996, Minshew et al., 1999, Minshew and Goldstein, 2001, Landa and Goldberg, 2005, Williams et al., 2005, Williams et al., 2006b, Joseph et al., 2005a, Joseph et al., 2005b, Verte et al., 2005, Nakahachi et al., 2006, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010, Yerys et al., 2012). There is a small body of conflicting evidence (Griffith et al., 1999, Ozonoff and Strayer, 2001) and the contrasting data in this area may be due to the differing cognitive demands of the task, as it has been observed that children with ASD exhibit their WM deficits under higher WM loads as they begin to reach their storage capacity (Landa and Goldberg, 2005, Steele et al., 2007, Cui et al., 2010). Further research using homogenous groups and well defined, challenging paradigms with as little loading on other executive functions as possible should be conducted in order to clarify the conflicting evidence regarding verbal WM deficits in children with ASD. The aforementioned N-Back task would be the ideal paradigm to address this

issue, particularly as WM load can be manipulated to make the task demanding enough for potential group differences to be observed.

1.2.3 – Summary of Working Memory in ADHD and ASD

The current literature provides strong evidence for the presence of a WM deficit in both children with ADHD (Stevens et al., 2002, Rhodes et al., 2005, Rhodes et al., 2012, Martinussen and Tannock, 2006, Klein et al., 2006, Rommelse et al., 2008, Rapport et al., 2008, Kofler et al., 2010, Toplak et al., 2009, Gibson et al., 2009, Barnett et al., 2009, Gau and Shang, 2010, Alderson et al., 2010, Wee et al., 2010, Crocker et al., 2011, Martinussen et al., 2005, Willcutt et al., 2005, Kasper et al., 2012) and children with ASD (Bennetto et al., 1996, Minshew and Goldstein, 2001, Minshew et al., 1999, Landa and Goldberg, 2005, Williams et al., 2005, Williams et al., 2006b, Joseph et al., 2005a, Joseph et al., 2005b, Verte et al., 2005, Nakahachi et al., 2006, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010, Yerys et al., 2012) compared to controls during tasks that assess both verbal and visuo-spatial storage, as well as the central executive component, of WM. Children and adolescents with ASD appear to be more impaired in visuo-spatial WM as oppose to verbal WM ((Minshew et al., 1999, Minshew and Goldstein, 2001, Landa and Goldberg, 2005, Williams et al., 2005, Williams et al., 2006b, Verte et al., 2005, Joseph et al., 2005a, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010) but there is evidence that the parametric aspect of the N-Back task is able to draw out subtle verbal memory difficulties in both ADHD (Klein et al., 2006, Pasini et al., 2007) and ASD (Cui et al., 2010). This makes it an ideal task to use in a study comparing the two disorders.

However, the only studies to directly compare ADHD and ASD have used visual-spatial WM tasks. These studies have yielded differing results, with some reporting that ASD children use poorer strategies and make more errors on the spatial WM and spatial span task of the CANTAB compared to both ADHD and typically developing children. In these studies, the children with ADHD were also impaired on the tasks compared to controls, suggesting that the WM deficit was shared between the two disorders, but more severe in ASD (Goldberg et al., 2005, Corbett et al.,

2009). There is also evidence to suggest that the WM deficit is specific to ADHD as it has been observed that children with ADHD make significantly more errors on the spatial WM task of the CANTAB compared to controls, while children with ASD do not differ from the ADHD or control group. (Happé et al., 2006). A few studies have reported no significant differences between ADHD, ASD or typically developing children during the spatial WM task of the CANTAB or the self-ordered pointing task (Sinzig et al., 2008, Geurts et al., 2004). Therefore, it would be of great interest to investigate verbal WM in a task such as the N-Back which has been shown to be effective in both ADHD (Klein et al., 2006, Pasini et al., 2007) and ASD (Cui et al., 2010) and which enables one to investigate the effect not only of WM, but of WM load as well.

1.3 – Motor and Interference Inhibition

1.3.1 – Motor Response Inhibition in ADHD

Motor response inhibition is defined as the ability to suppress a prepotent motor response (Barkley, 1997).

A task which is used to assess motor response inhibition is the Go/No-Go task. The Go/No-Go task requires a motor response to a Go signal and the inhibition of this response to a No-Go signal. The dependent measure is the probability of inhibition, which can also be expressed as commission errors (responses to the No-Go signal). Throughout the task, the percentage of Go signals is predominant and the No-Go signals are rare, ideally leading to a ratio of 70:30. Along with motor response inhibition, the Go/No-Go tasks also taps into response selection and decision making.

The Stop Signal task can also be used to assess motor response inhibition. During this task, the participant is told to respond to the presentation of a ‘go’ stimulus as quickly as they can by making a motor response, such as a button press. Throughout the course of this task, the subject will be randomly presented with infrequent ‘stop trials’, in either visual or auditory form, which will appear shortly

after the presentation of the go stimulus. In the traditional Stop Signal task the delay between go signal and stop signal is fixed by several delays of 250ms or 350ms. However, in order to prevent subjects from waiting for the predictable stop signal delay, a tracking Stop Signal task was created. The important aspect of the tracking Stop Signal task is that the delay between the presentation of the go stimulus and the presentation of the stop stimulus, which is initially set at 250ms, is individually altered after each stop trial to ensure that every subject inhibits in 50% of the trials. This makes the task equally difficult for every subject. The main performance measure of this task relies on the adjustable delay between the go stimulus and the stop stimulus. The Stop Signal Reaction Time (SSRT) is calculated by subtracting the mean stop signal delay time from the mean reaction time to go trials and a longer SSRT indicates poor inhibition (Logan et al., 1997).

The key difference between the Go/No-Go task and the Stop Signal task is that the Stop Signal task requires inhibition of an already triggered motor response and therefore contains a higher load on motor response inhibition. Logan, the creator of the Stop Signal task, described the process of motor response inhibition in the Stop Signal task as a race between two competing responses, one which aims to make a motor response, and the other which aims to prevent the already triggered motor response from occurring (Logan et al., 1997).

Due to the key role that difficulties in inhibition play in the diagnosis of ADHD (American et al., 1994), there is a wealth of research that uses these two tasks to investigate motor response inhibition in children with this disorder.

There is consistent evidence from neuropsychological studies that ADHD children have deficits in the Stop Signal task, as they have increased SSRTs (Rubia et al., 2001b, Rubia et al., 2007a, Martel et al., 2007, de Zeeuw et al., 2008, Lee et al., 2008, Luman et al., 2009). In addition, studies have also found abnormal Go process measures, such as increased mean reaction times and increased reaction time variability to go trials, and this variability is thought to be due to poor response preparation and lapses in attention throughout the task (Scheres et al., 2001, de Zeeuw et al., 2008, Vaurio et al., 2009, Luman et al., 2009).

Recent meta-analyses of the Stop Signal task have confirmed the presence of an inhibitory deficit in children with ADHD, as they have much longer SSRTs, the key indicator of poor inhibition during the task, as well as longer mean reaction times to go trials, compared to typically developing controls (Oosterlaan et al., 1998, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Lipszyc and Schachar, 2010).

There is also evidence for impaired performance in the Go/No-Go task in individuals with ADHD compared to controls (Oosterlaan et al., 1998, Overtom et al., 2002, Rubia et al., 1998, Rubia et al., 2001b, Rubia et al., 2007a, Wodka et al., 2007, Huang-Pollock et al., 2007).

1.3.2 – Interference Inhibition in ADHD

Another aspect of inhibition which has been investigated in ADHD is interference inhibition. Interference inhibition is described as the ability to suppress a dominant prepotent response in favour of a conflicting but correct response (Golden, 1978, Simon, 1990, Eriksen and Schultz, 1979). Three of the most well used tasks to assess this cognitive function are the Stroop Colour and Word task (Golden, 1978), which assesses verbal interference inhibition, the Eriksen Flanker Task and the Simon task, which both assess visuospatial interference inhibition (Simon, 1990, Eriksen and Schultz, 1979).

With regards to verbal interference inhibition, meta-analyses of the Stroop task in children with ADHD report mixed findings as poor colour naming and increased interference scores, relative to controls, have been previously reported (Homack and Riccio, 2004, Lansbergen et al., 2007). However, a meta-analysis of Stroop tasks in children and adults with ADHD found no evidence for impaired interference inhibition (Schwartz and Verhaeghen, 2008), and another meta-analysis in children with ADHD found that findings were dependent on the method used to calculate interference (Van Mourik et al., 2005).

Research into visuo-spatial interference inhibition has produced similarly conflicting results. Recent studies in children with ADHD have reported no deficit in

interference inhibition compared to controls on the Eriksen Flanker task (Adolfsson et al., 2008, Booth et al., 2007, Yordanova et al., 2011) or the Stroop task (Brocki et al., 2008, van Mourik et al., 2009, van Mourik et al., 2011). However, a recent review investigating interference inhibition in children with ADHD, as assessed by the Eriksen Flanker task and the Simon task, supported the presence of deficits in this cognitive domain in children with ADHD compared to controls (Mullane et al., 2009).

Thus, the current literature suggests that interference inhibition is not a key, consistent deficit in children with ADHD (Booth et al., 2007, Adolfsson et al., 2008, Brocki et al., 2008, van Mourik et al., 2009, van Mourik et al., 2011, Yordanova et al., 2011, Van Mourik et al., 2005, Schwartz and Verhaeghen, 2008).

1.3.3 – Motor Response and Interference Inhibition in ASD

There have been a number of studies investigating inhibition in ASD as it has been noted, at both a neuropsychological and a neurobiological level, that repetitive and restrictive behaviours may be linked to problems with inhibitory control (Lopez et al., 2005, Langen et al., 2011). The studies that have assessed inhibition in ASD have produced relatively mixed results, but the findings in this field become slightly more consistent once motor response inhibition and interference inhibition are viewed separately.

Studies focusing on motor response inhibition have found that children with ASD make more commission errors and have larger SSRTs than typical developing controls during Go/No-Go (Bishop and Norbury, 2005, Christ et al., 2007) and Stop Signal tasks (Verte et al., 2005, Lemon et al., 2011), respectively. Current reviews also support the presence of a deficit in prepotent response inhibition in ASD (Hill, 2004, Sanders et al., 2008, O'Hearn et al., 2008). However, there is also some evidence to suggest that motor response inhibition is intact in children with ASD (Ozonoff and Strayer, 1997, Raymaekers et al., 2006). The use of small sample sizes, altered versions of the Stop Signal task and the fact that the ADOS was not used to confirm current Autistic traits may account for the lack of findings in these studies.

Conflicting results have also been reported in interference inhibition. Research focusing on interference inhibition has produced evidence for task- specific deficits. Most studies report intact interference inhibition on Stroop tasks (Ozonoff and Jensen, 1999, Russell et al., 1999, Christ et al., 2007, Adams and Jarrold, 2009, Christ et al., 2011) apart from two studies reporting poor interference control in children with ASD compared to their typically developing peers (Verte et al., 2005, Robinson et al., 2009). It has been suggested that due to the lower levels of reading comprehension and reading ability in children with ASD, the word-colour interference of the Stroop task is less of an interference for this population compared to typically developing children of the same age (Adams and Jarrold, 2009). This is supported by the finding that, studies using Eriksen Flanker tasks and Simon tasks have reported impaired performance in children with ASD compared to controls (Christ et al., 2007, Christ et al., 2011, Hughes, 1996, Solomon et al., 2008, Tsai et al., 2011).

Hence, current research suggests that motor response inhibition (Bishop and Norbury, 2005, Verte et al., 2005, Christ et al., 2007, Lemon et al., 2011) and interference inhibition, as assessed using tasks with minimal reading or comprehension, is impaired in children with ASD compared to controls (Hughes, 1996, Solomon et al., 2008, Robinson et al., 2009, Christ et al., 2011, Tsai et al., 2011). However, the use of different paradigms, mixed sex groups and small sample sizes limit the reliability of these findings and all reviews in this area have commented on the need for more research to be conducted in order to elucidate the type of inhibitory deficit present in children with ASD (Hill, 2004, Sanders et al., 2008, O'Hearn et al., 2008). Therefore, research which investigates not only the cognitive aspect of inhibition, but also any underlying neurofunctional abnormalities, in a homogeneous sample of ASD individuals, may lead a clearer understanding of this deficit.

1.3.4 – Summary of Inhibition in ADHD and ASD

A number of studies have directly compared motor response inhibition between children with ADHD and children with ASD. These studies have reported mixed findings as some which have employed the Go/No-Go task have observed increased

omission and commission errors in children with ADHD, compared to children with ASD and typically developing children, while no difference in performance was observed between the ASD and control group (Happé et al., 2006, Sinzig et al., 2008). There have also been findings of no significant group differences between children with ADHD, children with ASD and controls using the Go/No-Go task (Raymaekers et al., 2007). However, using a Stop Signal task, it was observed that children with ADHD and ASD had significantly slower SSRTs compared to controls and that the two disorders were equally impaired (Geurts et al., 2004).

Thus, although the current literature in ADHD and ASD supports the presence of poor motor response inhibition in children with ADHD (Rubia et al., 2001b, Rubia et al., 2007a, Martel et al., 2007, de Zeeuw et al., 2008, Lee et al., 2008, Luman et al., 2009, Oosterlaan et al., 1998, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Lipszyc and Schachar, 2010) and children with ASD (Bishop and Norbury, 2005, Verte et al., 2005, Christ et al., 2007, Lemon et al., 2011), the extent to which these deficits are specific to ADHD, or are shared between the two disorders, has yet to be discerned. This is of vital importance as a greater understanding of the commonalities and disorder-specific differences in motor response inhibition between the two disorders has the potential to aid diagnosis.

Interference inhibition has the same potential, however the findings in this field are also conflicting, with some Stroop studies reporting that children with ASD are more impaired than children with ADHD and that both clinical groups are impaired compared to typically developing controls (Corbett et al., 2009). However, others have observed that ADHD children are specifically impaired in interference inhibition compared to ASD and control children, who perform equally as well each other (Ozonoff and Jensen, 1999). Equal performance between the ADHD, ASD and control groups has also been reported (Goldberg et al., 2005). A study using the Eriksen Flanker task found that children with ADHD performed worse than children with ASD and controls (Geurts et al., 2008). Due to the potential difficulties of using the Stroop Word-Colour task in children with ASD (Adams and Jarrold, 2009), future research should aim to use the Eriksen Flanker task in order to increase homogeneity in this field and produce more reliable results concerning the potential differential or

shared difficulties in interference inhibition in children with ADHD and children with ASD.

Both motor response and interference inhibition are important aspects of executive function which potentially play a role in ADHD and ASD behaviours (American et al., 1994). Therefore research is needed to shed light on whether these cognitive domains are impaired in both disorders and if so whether the neural correlates of this dysfunction are similar or distinct.

1.4 – Cognitive Flexibility

1.4.1 – Cognitive Flexibility in ADHD

Another executive which is thought to be impaired in both ADHD and ASD is cognitive flexibility. Cognitive flexibility is the ability of a person to change stimulus-response associations and adapt them based on feedback. One of the most common tasks for assessing cognitive flexibility is the Wisconsin Card Sorting Task (WCST) which requires participants to sort cards based on colour, shape or number, and after obtaining a string of correct responses the sorting rule is changed, unbeknown to the participant. They then have to adapt their behaviour to ascertain the new sorting rule and errors associated with continued selection of the previously correct rule are known as perseverative errors and are indicative of poor cognitive flexibility (Milner, 1963). However, as the WCST also taps into other executive functions such as WM and inhibition, and is dependent on IQ, there are other paradigms which test cognitive flexibility with less reliance on other executive functions.

There are other switching tasks that have lower demands on WM. Versions of the Meiran Switch Task are commonly used visuo-spatial cognitive flexibility tasks that require participants to change their motor response between a horizontal and vertical dimension depending on an instruction stimulus. This is seen in the Rubia adaptation of the Merian Switch task (Rubia et al., 2007a) as there is an arrow in the centre of the grid; if this arrow points to the side the participant must make a button

press to indicate which side of the screen the dot is on. If the arrow is pointing up or down the participant must make a button press to indicate whether the dot is in the upper or lower quadrant of the screen. These two types of trial are alternated throughout the task and the subject is required to switch their response accordingly (Meiran, 1996).

These types of tasks differ from reward reversal learning tasks, which also assess cognitive flexibility but require the participant to learn the stimulus-reward association and then reverse their response and select a previously non-rewarded stimulus that is now rewarded (Kehagia et al., 2010). The intra-dimensional/extra-dimensional (ID/ED) task of the CANTAB is a nine staged set shifting task of increasing difficulty. The task starts with the intra-dimensional aspect and this requires the participant to learn a stimulus-reward contingency between two pictures of colour filled shapes by selecting them with a button press and seeing which one produces positive feedback. This rule then reverses and the participant has to begin to choose the other, previously non-rewarded image. The difficulty of the task increases and as the stages get more challenging white lines are added to the images, and these extra-dimensional white lines become relevant for the stimulus-reward association (Robbins et al., 1994). This increasing difficulty enables the researcher to better assess the level of cognitive flexibility the participant is impaired in.

Increased perseverative responses on the WCST have been observed in a group of 35 medication naïve, non-comorbid boys with ADHD compared to controls (Marzocchi et al., 2008). However, Shimoni et al found no evidence of impairment in children with ADHD compared to controls while using a child friendly version of the WCST (Shimoni et al., 2012). The latter study used only a small age range of 8-11 years old and failed to comment on whether these children were medicated on the day of testing. Thus, these caveats may account for the lack of impairment observed.

Impaired cognitive flexibility in ADHD has also been observed during switching tasks. A switching task with a sustained attention component reported that children with ADHD made more commission errors during switch trials compared to repeated trials, relative to controls (Inoue et al., 2008). It has also been shown that

children with ADHD who have undergone a 48hr medication washout have increased reaction time variability, relative to controls, during a switch task and this was associated with symptom severity (Oades and Christiansen, 2008). Furthermore, poorer switching ability has been observed in unmedicated children with ADHD compared to their typically developing peers (Cepeda et al., 2000). However, a switching task with an element of interference inhibition found no impairment in the ADHD group relative to controls (Rommelse et al., 2007). Also, a study using the Meiran switch task only found a trend of impairment (Rubia et al., 2007a). This null finding may be due to the age range of the participants used, as their ages ranged from 8-19 years old. Furthermore, the fact that interference inhibition was intertwined with cognitive flexibility makes it difficult to state whether these null findings are truly reflective of intact cognitive flexibility in ADHD.

More consistent results have been reported in studies using the ID/ED in unmedicated children with ADHD, finding that they failed to complete as many stages, and took more trials to reach the criterion for each stage, compared to medicated ADHD children and controls (Kempton et al., 1999). Reversal tasks have also reported that children with ADHD who have had a 24hr washout take more trials to reach the criterion for reversal compared to controls (Itami and Uno, 2002).

Meta-analyses and reviews have also supported the presence of a deficit in cognitive flexibility in children with ADHD (Walshaw et al., 2010, Willcutt et al., 2005, Chamberlain et al., 2011) and this may be linked to some of the comorbidities between ADHD and ASD, as there is evidence that children with ASD also have impairments in cognitive flexibility.

1.4.2 – Cognitive Flexibility in ASD

As restricted and repetitive behaviours are one of the key diagnostic features of ASD, a large amount of neuropsychological research has been conducted in order to discern whether cognitive inflexibility is a key impairment in this disorder.

Studies employing the WCST have reported increased perservative errors, and a lack of significant strategy change with time, in children with ASD compared to typically developing controls (Ozonoff, 1995, Ozonoff and McEvoy, 1994, Ozonoff et al., 1991, Bennetto et al., 1996, Verte et al., 2005, Van Eylen et al., 2011).

Children with ASD also performed worse on the ID/ED task compared to their typically developing peers, as they completed fewer stages, took more trials to reach criterion in the later stages of the task and made more perservative errors (Hughes et al 1994). This finding of poorer performance in the extra-dimensional stages of the ID/ED task in children with Asperger's and children with ASD, compared to controls, has been replicated (Ozonoff et al., 2000, Yerys et al., 2009). It has also been reported that this increase in errors was correlated with repetitive behaviour (Yerys et al., 2009).

A lower percentage of shifting in children with ASD, relative to controls, has also been observed in simple switching tasks (Yerys et al., 2012); however, some studies have found no difference in performance between children with ASD and controls in these tasks (Poljac et al., 2010).

This cognitive inflexibility has also been observed during reversal learning tasks as studies using a spatial reversal task have reported increased perservative errors in children with ASD relative to typically developing controls (McEvoy et al., 1993, Coldren and Halloran, 2003, Yerys et al., 2007) as have studies using object discrimination reversal learning tasks (Loveland et al., 2008). There is also evidence to suggest that children with ASD have difficulties establishing stimulus-reward contingencies during reversal learning tasks (Zalla et al., 2009). Studies using young children, aged 3-4, have found no deficit in reversal learning in children with ASD, suggesting that this impairment becomes more evident with age (Lionello-DeNolf et al., 2008, Dawson et al., 2002). However, further research is needed to confirm this.

There is a wealth of evidence to support the presence of cognitive inflexibility in children and adolescents with ASD and this impairment can be elicited using a variety of cognitive flexibility tasks (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994,

Ozonoff, 1995, Ozonoff et al., 2000, McEvoy et al., 1993, Hughes et al., 1994, Bennetto et al., 1996, Coldren and Halloran, 2003, Verte et al., 2005, Yerys et al., 2007, Yerys et al., 2009, Yerys et al., 2012, Robinson et al., 2009, Van Eylen et al., 2011) alongside a number of negative findings (Geurts et al., 2009). However, the association between this cognitive deficit and ASD behaviours has yet to be fully explored. Future research should aim to investigate this potential association and try to shed light on the neural underpinnings of this cognitive deficit as this will help to increase our understanding about the link between brain dysfunction and behaviour in ASD.

1.4.3 – Summary of Cognitive Flexibility in ADHD and ASD

Studies using the WCST to directly compare cognitive flexibility in children with ADHD and children with ASD have found that children with ASD produce more perservative errors compared to both children with ADHD and controls, who do not differ from each other (Ozonoff and Jensen, 1999, Geurts et al., 2004). It has also been shown that children with ADHD and children with Pervasive Development Disorder – Not Otherwise Specified produce more total errors and achieved fewer categories compared to controls, and that the two patient groups did not differ from each other (Kado et al., 2012). A study by Tsuchiya et al showed that both the ADHD and ASD group produced more perservative responses compared to controls (Tsuchiya et al., 2005). However, the ADHD group produced more ‘Milner type’ perservative errors than both the control and ASD groups and these errors are described by the authors as responses which would have been correct in the preceding trial. They concluded that ADHD children had poorer cognitive flexibility than ASD children: however, as the WCST also taps in to inhibition processes the performance of ADHD children may be a combination of deficits in motor response inhibition and cognitive flexibility.

In contrast, studies using the ID/ED in children with ADHD and children with ASD found no significant differences between the patients and controls (Goldberg et al., 2005, Happe et al., 2006, Corbett et al., 2009) and this may be due to the relatively small sample sizes used.

Thus, although direct comparisons between ADHD and ASD have produced mixed results, there is strong evidence for cognitive inflexibility in children with ADHD (Kempton et al., 1999, Cepeda et al., 2000, Itami and Uno, 2002, Inoue et al., 2008, Oades and Christiansen, 2008, Marzocchi et al., 2008, Walshaw et al., 2010, Willcutt et al., 2005, Chamberlain et al., 2011) and children with ASD (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff, 1995, Ozonoff et al., 2000, McEvoy et al., 1993, Hughes et al., 1994, Bennetto et al., 1996, Coldren and Halloran, 2003, Verte et al., 2005, Yerys et al., 2007, Yerys et al., 2009, Yerys et al., 2012, Robinson et al., 2009, Van Eylen et al., 2011). However, studies using both children with ADHD and children with ASD have produced conflicting, and in the case of the ID/ED task null, results (Goldberg et al., 2005, Happe et al., 2006, Sinzig et al., 2008, Corbett et al., 2009). Future studies should focus on comparing these two neurodevelopmental disorders on reversal learning tasks as this paradigm has not been used to directly compare children with ADHD and children with ASD. It may produce clearer results, as it loads less onto other executive functions compared to the WCST and this may be the reason why unclear results have been obtained in studies using the WCST. Furthermore, the use of small, heterogeneous groups in the studies using the ID/ED may have led to the null findings observed. The use of larger, homogeneous groups will help to rectify these caveats and produce more reliable results.

1.5 – Other Cognitive Domains

1.5.1 – ADHD

In order to understand the full psychological profile of both ADHD and ASD, and gain a holistic view of both complex disorders, the other main cognitive domains of impairment will be briefly discussed.

Children with ADHD also exhibit deficits in executive function domains other than those previously reviewed, particularly in sustained attention. Sustained attention is defined as the ability to voluntarily attend to a specific, infrequent stimuli (Parasuraman et al., 1998). It has been consistently reported that children with ADHD

make more omission and commission errors relative to controls during classic vigilance tasks such as the Continuous Performance Task (Willcutt et al., 2005, Gualtieri and Johnson, 2008, Klein et al., 2006, Rubia et al., 2007a).

In addition, it has been reported that children with ADHD are impaired in tasks of temporal discounting. Temporal discounting refers to the relative value of a reward based upon the length of time the reward is delayed for (Sonuga-Barke et al., 2003). Children with ADHD have difficulty delaying reward and will choose small immediate rewards over larger delayed rewards significantly more than their aged matched peers (Solanto et al., 2001, Thorell, 2007, Bitsakou et al., 2009, Marco et al., 2009, Scheres et al., 2010). It has been hypothesised that this ‘delay aversion’ may play a key role in the behaviours observed in ADHD (Sonuga-Barke, 2003). It has also been shown that children with ADHD exhibit difficulties in other hot executive functions because they have altered sensitivity to reward during tasks that involve reward and/or motivation, such as temporal discounting and gambling tasks (Solanto et al., 2001, Toplak et al., 2006, Thorell, 2007, Garon et al., 2006, Luman et al., 2010, Scheres et al., 2010).

Furthermore, there is compelling evidence to support the presence of motor timing and time perception deficits in children with ADHD, as it has been repeatedly shown that children with ADHD have problems with fine temporal discrimination and time reproduction (Toplak et al., 2006, Rubia et al., 2009a, Noreika et al., 2013).

1.5.2 – ASD

While children with ASD show executive dysfunction, and there is evidence to suggest that this impairment plays a vital role in the aetiology of ASD (Hughes et al., 1994, Ozonoff et al., 2004, Hill, 2004, Geurts et al., 2004, Corbett et al., 2009), individuals with ASD have more consistently been associated with deficits in other cognitive and social domains. There is evidence that ASD patients are impaired in Theory of Mind (ToM). ToM is described as the ability to understand, and empathise with, the mental state of others and it has been shown that individuals with ASD are

impaired in this skill (Baron-Cohen and Laraine Masters, 2000, Baron-Cohen et al., 1985, Frith, 1994, Joseph and Tager-Flusberg, 2004, Tager-Flusberg, 2007).

It has also been argued that differences in central coherence, the ability to assess information as a whole and focus less on the finer details in order to understand the general meaning, may play a part in the clinical symptoms of ASD (Happé, 1997, Pellicano et al., 2006, Booth and Happé, 2010).

1.6 – Overall conclusions

There is evidence that both children with ADHD (Stevens et al., 2002, Rhodes et al., 2005, Rhodes et al., 2012, Martinussen and Tannock, 2006, Klein et al., 2006, Rommelse et al., 2008, Rapport et al., 2008, Kofler et al., 2010, Toplak et al., 2009, Gibson et al., 2009, Barnett et al., 2009, Gau and Shang, 2010, Alderson et al., 2010, Wee et al., 2010, Crocker et al., 2011, Martinussen et al., 2005, Willcutt et al., 2005, Kasper et al., 2012) and children with ASD (Bennetto et al., 1996, Minshew and Goldstein, 2001, Minshew et al., 1999, Landa and Goldberg, 2005, Williams et al., 2005, Williams et al., 2006b, Joseph et al., 2005a, Joseph et al., 2005b, Verte et al., 2005, Nakahachi et al., 2006, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010, Yerys et al., 2012) are impaired in all components of the Baddley model of WM compared to typically developing controls. Although a number of neuropsychological studies have compared visuo-spatial WM in ADHD and ASD (Geurts et al., 2004, Goldberg et al., 2005, Happe et al., 2006, Corbett et al., 2009, Sinzig et al., 2008), they have produced mixed results and this may be due to the small sample sizes and heterogeneity present in the studies. Furthermore, none have investigated verbal WM in a homogeneous group of children with ADHD and children with ASD to ascertain whether more consistent results are obtained using this WM domain. A parametric N-Back task would be an ideal paradigm to use in a study comparing these two disorders as it has been shown to tap into impairments in both children with ADHD (Klein et al., 2006, Pasini et al., 2007) and children with ASD (Cui et al., 2010) and it also enables one to investigate the effect of WM load, which has also never been compared between the two disorders.

In addition to WM, motor response inhibition and interference inhibition are areas of significant cognitive deficit in children with ADHD (Rubia et al., 2001b, Rubia et al., 2007a, Martel et al., 2007, de Zeeuw et al., 2008, Lee et al., 2008, Luman et al., 2009, Oosterlaan et al., 1998, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Lipszyc and Schachar, 2010) and there is research to support the presence of poor motor response inhibition in children with ASD compared to controls (Bishop and Norbury, 2005, Verte et al., 2005, Christ et al., 2007, Lemon et al., 2011). As with studies assessing WM in both ADHD and ASD, small sample sizes and group heterogeneity may have led to the mixed results reported in studies which investigate motor response inhibition and interference inhibition in these two disorders (Ozonoff and Jensen, 1999, Geurts et al., 2004, Geurts et al., 2008, Goldberg et al., 2005, Happe et al., 2006, Corbett et al., 2009). When focusing on studies of motor response inhibition, as the evidence for deficits in both ADHD and ASD is stronger in this domain compared to interference inhibition, those using the Go/No-Go found only deficits between ADHD compared to ASD and control children (Happe et al., 2006, Sinzig et al., 2008) or in one study no difference at all (Raymaekers et al., 2007). By contrast, a study using the Stop Signal task found that both groups were impaired compared to controls and that the patient groups did not differ from each other (Geurts et al., 2004). This suggests that the more difficult tracking Stop Signal task, tapping into withdrawal of an already triggered motor response, is better suited to detect deficits in motor response inhibition in children with ADHD and children with ASD than the easier Go/No-Go task.

Cognitive flexibility is another important executive function and it has been shown that children with ADHD (Kempton et al., 1999, Cepeda et al., 2000, Itami and Uno, 2002, Inoue et al., 2008, Oades and Christiansen, 2008, Marzocchi et al., 2008, Walshaw et al., 2010, Willcutt et al., 2005, Chamberlain et al., 2011) and children with ASD (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff, 1995, Ozonoff et al., 2000, McEvoy et al., 1993, Hughes et al., 1994, Bennetto et al., 1996, Coldren and Halloran, 2003, Verte et al., 2005, Yerys et al., 2007, Yerys et al., 2009, Yerys et al., 2012, Robinson et al., 2009, Van Eylen et al., 2011), both have difficulties in this domain as evidenced by their perservative responses in a variety of tasks assessing cognitive flexibility. Research focused on investigating the comparative levels of cognitive inflexibility in these disorders has produced conflicting results, with studies

using the ID/ED reporting no deficits between either the patient groups or controls (Goldberg et al., 2005, Happe et al., 2006, Sinzig et al., 2008, Corbett et al., 2009). However, there is evidence for ASD specific deficits compared to typically developing and ADHD children in this domain using the WCST (Ozonoff and Jensen, 1999, Geurts et al., 2004). These findings may be the result of type of task being used as both the WCST and ID/ED tap into other cognitive functions. Previous studies of both children with ADHD and children with ASD have not yet employed a reward reversal learning task and it would be intriguing to see whether reward reversal learning is able to uncover the differential deficits in cognitive flexibility in children with ADHD and children with ASD.

In conclusion, although there is a wealth of literature supporting the presence of executive function deficits in children with ADHD and children with ASD in tasks of WM, motor response inhibition and cognitive flexibility, studies directly comparing the two disorders produce incongruent results. These conflicting results may be due to the small, heterogeneous groups used as well as the different paradigms employed. The changes to DSM-IV which will allow co-diagnosis of ASD and ADHD highlight the relevance and importance of research which aims to uncover the shared and disorder-specific impairments in children with these disorders.

Therefore, it is paramount to compare large, pure groups of children with ADHD and children with ASD in tasks of WM, motor response inhibition and reward reversal learning, as it has been shown that these cognitive domains are particularly impaired, and therefore particularly pertinent, to these disorders.

Chapter 2 – Brain Structure Abnormalities in ADHD and ASD

2.1 – Introduction

In previous studies, it had been observed that individuals suffering from lesions of the prefrontal cortex often displayed deficits in executive functions such as WM, inhibition and cognitive flexibility (Owen et al., 1990, Aron et al., 2003, Milner, 1963). This led to the hypothesis that the neural basis of executive functions might lie in the prefrontal cortex (Miller and Cohen, 2001, Poldrack et al., 2011). As the cognitive impairments observed in these neurological studies mirrored those reported in ADHD and ASD, researchers began to postulate that the cognitive deficits in both ADHD and ASD might be due to abnormalities in the prefrontal cortex. However, the only way in which this hypothesis could be investigated in vivo was by the use of neuroimaging techniques. Neuroimaging is the process of imaging and measuring the structure, function and biochemistry of the brain. The only way of obtaining in vivo structural data about the brain using non ionising radiation is by a technique known as structural magnetic resonance imaging (sMRI) it fast became one of the more popular methods of neuroimaging (Poldrack et al., 2011).

sMRI often focuses on the two main components of the brain, known as white matter and grey matter. White matter refers to the axon extending from a neuron, while grey matter refers to the cell body of the neuron (Kandel et al., 2000). Research into the developmental trajectory of brain structure using sMRI has found that there is a linear increase in white matter during childhood and adolescence up to mid-adulthood (Paus et al., 2001). This increase is associated with an increase in myelination that speeds up information transfer between neurons and improves white matter integrity, indicating increased connectivity within the brain which then allows for more integrated and co-ordinated responses with increasing age (Giedd and Rapoport, 2010, Blakemore, 2011). Conversely, it has been found that grey matter has an inverted-U shape trajectory, where it increases with age, peaks in adolescence, and declines in adulthood; this has been attributed to the synaptic proliferation that occurs in childhood and early adolescence which is then followed by neuronal ‘pruning’ in

later adolescence and early adulthood (Giedd and Rapoport, 2010, Blakemore, 2011). Therefore, with age we see not only an increase in the ability to transfer information within the brain, but a refining of the information itself. It has also been reported that subcortical limbic areas reach structural maturity much earlier than the frontal brain regions involved in executive function, and it is known that dorsolateral prefrontal cortex (DLPFC) is one of the last regions of the brain to reach full maturity (Paus et al., 1999, Casey and Jones, 2010). A linear correlation has been observed between structural development, particularly of the prefrontal cortex, and executive function processes such as inhibition, planning and cognitive flexibility (Casey and Jones, 2010, Giedd and Rapoport, 2010, Blakemore, 2011). Therefore, abnormalities or delays in the development of brain structure and function may play a role in the executive dysfunction observed in ADHD and ASD. Consequently, it is important to understand the neuroanatomical differences present in ADHD and ASD, as they may shed light on the potentially shared or disorder-specific biological bases of the cognitive impairments in these disorders and provide potential diagnostic markers.

2.2 – Brain Structure Abnormalities

2.2.1 – Brain Structure Abnormalities in ADHD

It has been consistently observed that both medicated (Mostofsky et al., 2002, Hill et al., 2003, Carmona et al., 2005, Wolosin et al., 2009, Batty et al., 2010) and medication naïve (Castellanos et al., 2002) ADHD children show significantly reduced total cerebral volumes compared to their typically developing peers. Decreased total white matter and decreased total grey matter has also been reported in children with ADHD compared to controls (Filipek et al., 1997, Overmeyer et al., 2001, Mostofsky et al., 2002, Sowell et al., 2003b, Carmona et al., 2005, Batty et al., 2010, Qiu et al., 2011), and there is evidence to suggest that there may be a laterality effect of these white and grey matter abnormalities, with white matter deficits being more left hemispheric and grey matter deficits being more right hemispheric (Overmeyer et al., 2001, Mostofsky et al., 2002). This is suggestive of poor interactions between left hemispheric language networks and immature signalling in

right hemispheric visuo-spatial attention networks (Hervé et al., 2013), the latter of which may play a role in the poor sustained attention observed in ADHD.

When focusing on the frontal lobe, it has been repeatedly reported that children with ADHD have decreased total, grey and white matter volumes relative to age matched controls (Filipek et al., 1997, Overmeyer et al., 2001, Castellanos et al., 2002, Sowell et al., 2003b, Hill et al., 2003, Durston et al., 2004, Carmona et al., 2005, McAlonan et al., 2007, Depue et al., 2010a). One whole brain, cross-sectional study reported that the decreased white and grey matter in the frontal lobe accounted for 48% of the total decrease in cerebral volume. This highlights the large role that the neuroanatomical deficits of the frontal lobe play in the overall structural differences observed in the cerebrum of children with ADHD compared to controls (Mostofsky et al., 2002). Furthermore, it has been shown in an impressive whole brain longitudinal study, which spanned over a decade and consisted of 152 ADHD children, that decreased frontal grey matter was linked to worse ADHD symptoms (Castellanos et al., 2002). Hence, the structural anatomy of the frontal lobe atypical in children with ADHD and this may play a role in the executive dysfunction reported present in this population.

This potential link between structural abnormalities in frontal lobe and impaired executive function has been supported in a region of interest (ROI) study focusing on right inferior frontal cortex (IFC) (Depue et al., 2010a). This study found decreased grey matter (Depue et al., 2010a) in 31 medicated, older adolescents with ADHD when they were compared to age matched controls. A Digit Span Symbol test, a Continuous Performance Task and a Stop Signal task were used in order to assess processing speed, inhibition and response variability between groups. It was noted that the decrease in right IFC grey matter was positively correlated with processing speed and negatively correlated with commission errors on the Continuous Performance Task, Stop Signal Reaction Times and response variability. This indicated that less grey matter in this area was linked to poorer performance in neuropsychological domains that individuals with ADHD are normally impaired in (Losier et al., 1996, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Adams et al., 2008). This finding is highly pertinent, as it is known that right IFC is a key area for motor response inhibition (Rubia et al., 2001a, Rubia et al., 2003, Rubia

et al., 2006, Rubia et al., 2007c, Aron and Poldrack, 2006, Chevrier et al., 2007, Simmonds et al., 2008, Chambers et al., 2009).

Neuroanatomical abnormalities have also been reported in other frontal regions that play a role in executive functions. Decreased total and grey matter volume has been observed in superior frontal cortex (Filipek et al., 1997, Overmeyer et al., 2001, Hill et al., 2003) while decreased local size has been observed in inferior DLPFC (Sowell et al., 2003b), and decreased grey matter in the anterior cingulate cortex (ACC) (Carmona et al., 2005) of children with ADHD compared to controls.

These findings highlight the significant neuroanatomical differences between children and older adolescents with ADHD and their typical developing peers in frontal lobe regions that are vital for executive functions, as well as supporting the hypothesis that these structural abnormalities are linked to the symptoms of ADHD (Filipek et al., 1997, Overmeyer et al., 2001, Castellanos et al., 2002, Sowell et al., 2003b, Hill et al., 2003, Durston et al., 2004, Carmona et al., 2005, McAlonan et al., 2007, Garrett et al., 2008, Depue et al., 2010a). This is highly relevant to this thesis because these neuroanatomical differences may result in abnormal neurofunctional activity in these brain regions.

Although the frontal lobe is intrinsic to executive function, it is not the only region involved in these processes. The basal ganglia are highly connected to the prefrontal cortex and it is known that they play an integral role in areas of executive function that individuals with ADHD are impaired in such as motor response inhibition and temporal discounting (Rubia et al., 2007c, McNab and Klingberg, 2008, Tanaka et al., 2004, Chambers et al., 2009). Consequently, abnormalities in these subcortical structures may also be linked to some of the executive dysfunctions that are reported in ADHD.

Decreased volume has been observed consistently in both the head, body and total caudate, in children with ADHD compared to controls in both cross-sectional (Filipek et al., 1997, Tremols et al., 2008, Garrett et al., 2008, Carrey et al., 2012) and longitudinal studies (Castellanos et al., 2002). These structural abnormalities in the caudate have been linked to more severe forms of ADHD (Castellanos et al., 2002)

and better medication response (Filipek et al., 1997). It has also been noted that the symmetry of the caudate differs between controls and children with ADHD as there is evidence that children with ADHD exhibit more asymmetrical (Tremols et al., 2008), and more symmetrical caudate volumes (Filipek et al., 1997). However, some studies have shown that these differences are age dependent.

A longitudinal study of 152 children with ADHD showed that differences in total caudate volume normalise by adolescence, relative to controls (Castellanos et al., 2002). A recent cross-sectional ROI study reported that in 26 medication naïve boys with combined type ADHD, the younger subgroup of the cohort (aged 5.9-7.3) was driving the overall group differences in caudate volume between ADHD and controls (Carrey et al., 2012). The medication naivety and homogeneity of the ADHD group in Carrey et al's study make these findings reliable and they have been supported by a recent meta-analysis conducted on 378 individuals with ADHD and 344 controls which found that caudate and right lentiform nucleus abnormalities in ADHD normalised with age and stimulant medication (Nakao et al., 2011, Frodl and Skokauskas, 2012). These findings suggest that the structure of the caudate may play an integral role in ADHD symptomology, and that the decrease in ADHD symptoms with both medication and age may be mediated by normalisation of this subcortical brain region. This is of particular pertinence to this thesis as these structural abnormalities may result in impaired neurofunctional activity of the caudate.

Structural abnormalities have also been reported in other areas of the basal ganglia such as the globus pallidus and ventral striatum. Whole brain studies have reported decreased grey matter in the globus pallidus (Overmeyer et al., 2001, McAlonan et al., 2007). However, in McAlonan et al's study, when comorbidity with ODD and CD was removed from the ADHD group, the globus pallidus findings were no longer significant, highlighting the importance of using non-comorbid groups. Decreased grey matter has also been reported in right putamen, as has decreased volume in bilateral anterior putamen and increased volume in posterior putamen (Overmeyer et al., 2001).

Only one cross-sectional, ROI study using 42 mainly medicated ADHD children of mixed sex and subtype, found decreased total ventro-striatal volume relative to

control children (Carmona et al., 2009). They also observed that decreased ventro-striatal volume was correlated with increased hyperactive and inattentive scores. Given the role of ventral striatum in reward (Fareri et al., 2008), and the hypothesis that hyperactivity and inattention in ADHD are the result of an delay aversion to delayed rewards (Sonuga-Barke, 2003), these findings are highly intriguing. However, further research is needed to clarify this, particularly with regards to small subcortical structures such as the ventral striatum.

Unlike the frontal lobe and basal ganglia, the cerebellum was initially thought to be involved in motor skills only, and was therefore relatively under researched in ADHD. However, it has now been established that it plays a role in executive functions that are impaired in ADHD such as attention and timing (Riva and Giorgi, 2000, Schmahmann and Caplan, 2006, Bellebaum and Daum, 2007, Timmann and Daum, 2007). This therefore makes the consistent findings of structural abnormalities in this region in children with ADHD particularly pertinent. Decreased cerebellar volumes have been reported in total cerebellum, (Castellanos et al., 2002, Durston et al., 2004) superior vermis of the cerebellum (Mackie et al., 2007), the inferior posterior vermis of the cerebellum (Berquin et al., 1998, Bledsoe et al., 2009) and cerebellar lobes I-V and VIII-X (Hill et al., 2003, Seidman et al., 2005), in children with ADHD compared to controls. It has also been observed in two longitudinal studies that decreased total volume of the cerebellum in children with ADHD is correlated with increased ADHD symptoms (Castellanos et al., 2002) and that a developmental trajectory that leads to a progressive total decrease in cerebellar volume is correlated with worse clinical outcomes (Mackie et al., 2007). This suggests that a continuation of total cerebellar volume decrease throughout development maybe be key in identifying the ADHD children whose ADHD persists into adulthood.

Neuroanatomical differences have also been observed in other regions of the brain. The majority of studies that observe structural abnormalities of the temporal lobe in children with ADHD report decreased grey matter (Castellanos et al., 2002, Sowell et al., 2003b, Carmona et al., 2005, Sasayama et al., 2010) and white matter volume (McAlonan et al., 2007) compared to controls. However, there is evidence for

increased grey matter in posterior temporal lobe in ADHD children relative to typical developing children (Sowell et al., 2003b).

There is also evidence for both increased (Sowell et al., 2003b) and decreased (McAlonan et al., 2007) grey matter volume in inferior parietal lobe. The fact that Sowell et al included 11 girls in their ADHD group, which had a total of 27, while McAlonan et al used an all boy sample of 28, may account for the incongruity of these findings. Decreased grey matter has also been reported in right superior parietal lobe in young adults with ADHD compared to age matched controls, and this abnormality has been shown to correlate with increased response variability (Depue et al., 2010a). This suggests that there may be a link between the structure of superior parietal lobe, a key area for attentional orientation (Bisley and Goldberg, 2010) and lapses in attention in ADHD.

Abnormalities in the neuroanatomy of the occipital lobe have also been observed in children with ADHD compared to controls, particularly decreased grey matter volume in left occipital lobe (Sowell et al., 2003b, McAlonan et al., 2007, Sasayama et al., 2010), with some evidence for white matter volume reduction also (Durstun et al., 2004). One study noted that this decrease in grey matter volume was correlated with inattention scores (Sowell et al., 2003b). However more research is needed to corroborate these findings.

Areas of the limbic system have also been reported to be structurally abnormal in older adolescents and children with ADHD compared to aged matched controls, as decreased grey matter volume has been observed in anterior insula and amygdala. (Lopez-Larson et al., 2009, Depue et al., 2010a, Lopez-Larson et al., 2012). Furthermore, decreased grey matter volume in the anterior insula has been shown to correlate with poorer processing speed (Depue et al., 2010a).

Understanding the interhemispheric connection between these structurally abnormal brain regions is of great importance because aberrant connectivity leads to mal co-ordinated brain responses. The corpus callosum has the vital role of connecting both hemispheres and is one of the largest white matter tracts in the brain (Bloom and Hynd, 2005). There is a large body of evidence to show that there are

abnormalities in the corpus callosum of children with ADHD compared to controls, as reduced volume, surface area, thickness and fibre organisation of this white matter tract have been reported (McAlonan et al., 2007, Hill et al., 2003, Luders et al., 2009, Cao et al., 2010). A meta-analysis of 13 studies focusing on the corpus callosum in ADHD found that children and adolescents have a smaller splenium; this result is largely attributable to the females with ADHD as boys with ADHD were found to have smaller rostral bodies (Hutchinson et al., 2008). In addition to these cross-sectional structural differences, abnormalities in the development of the corpus callosum have been reported. It has been observed in a longitudinal study of 236 children with ADHD, predominantly right handed, that there is an increased growth rate in anterior corpus callosum compared to controls, and the authors propose that this may be linked to some of the differences in cortical asymmetry reported in children with ADHD (Gilliam et al., 2011, Shaw et al., 2009a). However, more longitudinal studies are needed to understand how this increase in corpus callosal growth ties in with the consistent reports of reduced volume, thickness and area (McAlonan et al., 2007, Hill et al., 2003, Luders et al., 2009, Cao et al., 2010, Schnoebelen et al., 2010, Hutchinson et al., 2008).

Thickness of the cortex itself has also been investigated in children with ADHD and has yielded intriguing results. The cortex is described as the neuronal layer of cells present on the surface of the brain and the developmental trajectory of the thickness of this layer has been shown to correlate with IQ (Kandel et al., 2000, Shaw et al., 2006a).

One of the first studies to assess this neuroanatomical construct in children with ADHD was a longitudinal study by Shaw et al 2006. They observed that in 163 children with mainly combined type ADHD there was significant cortical thinning across the whole brain compared to typically developing children, particularly in bilateral medial prefrontal cortex (mPFC), bilateral superior frontal cortex, left precentral and right mesial temporal. When these structural differences were investigated with regards to clinical outcome it was noted that thinner mPFC, cingulate and superior frontal cortices were correlated with worse clinical outcome as defined by DSM-IV and Childrens Global Assessment Scale and that normalisation of

cortical thickness in right parietal lobe at age 17 was associated with better outcome and remission and ADHD symptoms.

This finding was supported by another longitudinal study by Shaw et al 2007 (Shaw et al., 2007). This found that, although the pattern of development was similar between children with ADHD and healthy controls, children with ADHD reached peak cortical thickness in 50% of the cortical points significantly later than controls, particularly in middle/superior frontal cortices, mPFC and middle/superior temporal lobe. Earlier peak thicknesses in primary motor cortices were also reported in children with ADHD. Cross-sectional studies have supported these longitudinal findings of decreased frontal and increased motor cortex thickness and have found these structural abnormalities to be linked to an increased number of DSM-IV ADHD criteria (Narr et al., 2009, Almeida et al., 2010, Almeida Montes et al., 2012, Duerden et al., 2012). This has led to the hypothesis that children with ADHD have delayed cortical maturation and that this may play a role in their age inappropriate behaviour.

In order to gain a holistic look at the neuroanatomical abnormalities reported in ADHD a number of meta-analyses have been conducted (Valera et al., 2007, Ellison-Wright and Ellison-Wright, 2008, Frodl and Skokauskas, 2012, Nakao et al., 2011). Earlier meta-analyses using ROIs found decreased total cerebellar, cerebral, right caudate and splenium of the corpus callosum volume in children and adults with ADHD (Valera et al., 2007). However, more recent whole brain meta-analyses have found grey matter reduction in bilateral putamen/globus pallidus and decreased grey matter and total volume of the caudate in children and adults with ADHD (Ellison-Wright and Ellison-Wright, 2008, Frodl and Skokauskas, 2012, Nakao et al., 2011). Nakao et al conducted meta-regressions on age and medication and found that increasing age and stimulant medication use was associated with grey matter in right lentiform nucleus and caudate (Nakao et al., 2011). This mirrors the findings of reduced structural abnormalities in the caudate with increasing age that were reported by Castellanos et al (2002) and Carrey et al (2012). One of the meta-analyses also observed increased grey matter in left posterior cingulate cortex (PCC) in ADHD relative to controls (Nakao et al., 2011).

The findings of these individual studies and meta-analyses provide consistent evidence for a reduction in total cerebral, cerebellar and basal ganglia volumes, as well as reduced cortical thickness in several regions, in particular frontal lobe, parietal lobe and temporal lobe in children with ADHD compared to controls (Filipek et al., 1997, Castellanos et al., 2002, Mostofsky et al., 2002, Hill et al., 2003, Durston et al., 2004, Carmona et al., 2005, Shaw et al., 2006b, Shaw et al., 2007, Tremols et al., 2008, Garrett et al., 2008, Wolosin et al., 2009, Qiu et al., 2009, Narr et al., 2009, Batty et al., 2010, Almeida et al., 2010, Nakao et al., 2011, Carrey et al., 2012, Almeida Montes et al., 2012, Frodl and Skokauskas, 2012). There is also interesting evidence to support the link between neuroanatomical abnormalities in children with ADHD and ADHD symptom severity (Castellanos et al., 2002, Sowell et al., 2003b, Mackie et al., 2007, Carmona et al., 2009, Depue et al., 2010a, Almeida et al., 2010, Almeida Montes et al., 2012) as well as the role of the normalisation of these structural differences in the remission and persistence of these symptoms (Castellanos et al., 2002, Mackie et al., 2007). Consistent evidence for smaller volume and area of the corpus callosum in children with ADHD compared to typically developing children has also been reported (Hill et al., 2003, McAlonan et al., 2007, Luders et al., 2009, Cao et al., 2010, Roessner et al., 2004, Schnoebelen et al., 2010, Hutchinson et al., 2008). However, the key findings that are of particular relevance to ADHD are the structural abnormalities in prefrontal cortex, caudate and cerebellum, as these structures play an integral role in the executive functions that are impaired in ADHD and there is evidence that these abnormalities are linked to ADHD behaviour and persistence (Castellanos et al., 2002, Mackie et al., 2007, Depue et al., 2010a). However, there are many caveats of the studies reviewed above; namely, the use of small, previously medicated, comorbid, mixed sex patient groups, as all of these factors have been shown to have an effect on brain structure (Shaw et al., 2009b, McAlonan et al., 2007, Luders et al., 2003, Cosgrove et al., 2007, Kanner, 1943). This highlights the need for more studies in this field that use homogeneous, one-sex, non-comorbid and medication-naïve groups, as important but subtle structural differences may be being masked by the confounds mentioned above.

2.2.2 – Brain Structure Abnormalities in ASD

Leo Kanner described the presence of abnormally “large heads” in 5 of the 11 case studies he reported in his seminal paper of 1943 (Kanner, 1943). This was the first, albeit qualitative, evidence that abnormal brain structure may be present in Autism. Further research into this area found that approximately 20-40% of young children with ASD can be classified as having macrocephaly, which is defined as a head circumference above the 97th percentile (Acosta and Pearl, 2004, Mosconi et al., 2006, Verhoeven et al., 2009, Stigler et al., 2011). However, it was not until the advent of sMRI that the biological basis of these findings could be investigated.

A landmark paper by Courchesne et al showed that at birth 30 boys with Autism had a normal head circumference, but by age 2-4, 90% of the sample had a larger than normal brain volume with 34% being classified as macrocephalic (Courchesne et al., 2001). Further research indicated that in boys aged 2-3 years old there was an increase in cerebral grey matter volume and white matter volume, 12% and 18% respectively, in addition to a 39% increase in cerebellar white matter. However, none of these abnormalities were present in the 30 older autistic boys, aged 12-16, who were also scanned. From these findings the authors proposed that Autism is characterised by a post-natal increase in brain growth which then slows down through development, leading to normalisation by adolescence. A number of studies have provided evidence for increased total brain volume (Sparks et al., 2002, Nordahl et al., 2012), and total grey matter volume (Calderoni et al., 2012), in children aged 2-7 with ASD which supports this hypothesis and is of particular interest as this overgrowth occurs at the same point in development that Autistic traits become apparent (American et al., 1994). However, there is also evidence of increased brain volume, grey matter volume and white matter volume in some, but not all, adolescents and adults with ASD (Piven et al., 1992, Palmen et al., 2005, Hazlett et al., 2006, Brun et al., 2009, Freitag et al., 2009) which questions the progressive normalisation that is proposed to occur with increasing age. This inconsistency draws to light the fact that more longitudinal studies are needed to clarify the developmental trajectory of the neuroanatomy of the Autistic brain.

Structural abnormalities have also been observed in children and adolescents with ASD. Increased total volume has been observed in the frontal lobe, particularly in the DLPFC (Waiter et al., 2004, Carper and Courchesne, 2005, Hazlett et al., 2006, Brun et al., 2009, Mitchell et al., 2009b, Stigler et al., 2011) as well as increased grey matter volume in mPFC, ACC, DLPFC and left superior frontal cortex (Waiter et al., 2004, Bonilha et al., 2008, Calderoni et al., 2012) in both children and adolescents with ASD compared to controls. Furthermore, it has been observed in a cross-sectional ROI study that this increased DLPFC volume was associated with increased Autism severity as assessed by the Autism Diagnostic Observation Schedule (ADOS) in both young children and adolescents with ASD (Mitchell et al., 2009b). However, decreases in grey matter volume in adolescents with ASD have also been reported in right orbitofrontal cortex (OFC), IFC and middle frontal cortex and the body of the cingulate cortex relative to controls (Kwon et al., 2004, McAlonan et al., 2005). This suggests that late developing areas such as DLPFC may be particularly abnormal in ASD and that this may be related to ASD symptoms. This is of particular relevance to this thesis because it is known that DLPFC is involved in WM (Wager and Smith, 2003).

It has also been shown that the cerebellum has a role in WM (Timmann and Daum, 2007) and the neuroanatomy of this area in ASD has long been a point of interest. An early sMRI paper reported decreased volume in cerebellar vermis lobules VI-VII in 18 children and adults with Autism, and although a few studies have been able to replicate this finding (Courchesne et al., 1988, Courchesne et al., 1994, Courchesne et al., 2001), several were unable to do so (Piven et al., 1992, Hashimoto et al., 1992, Holttum et al., 1992). This inconsistency may be due to the large age ranges that were used in some of the studies, and there may be subgroups within ASD that are characterised by either significantly larger (hyperplasia), or significantly smaller (hypoplasia), cerebellar vermi as evidenced in Courchesne et al (1994). Studies focusing solely on children and adolescents have found both increased (Sparks et al., 2002, Palmen et al., 2005, Bonilha et al., 2008) and decreased total cerebellar volumes, grey matter volumes and white matter volumes compared to controls, as well as decreased total cerebellar vermis volume (Courchesne et al., 2001, Brun et al., 2009, Webb et al., 2009). These differing findings highlight the need for more research to be conducted separately in child, adolescent and adult populations of

ASD focusing on the cerebellum as a whole, as well as the vermis, in order to help advance our knowledge of this brain region and its role in ASD.

The basal ganglia and thalamus are areas of the brain that are not often focused upon in ASD, despite evidence for their roles in restrictive and repetitive behaviours (Langen et al., 2011). However, an ROI study found increased total volume of the caudate in 38 children and adolescents with ASD compared to controls and this increased volume was correlated with poorer performance on the WCST, increased impulsivity and increased omission errors on the Continuous Performance Task (Voelbel et al., 2006). Decreased grey matter volume has also been observed in children and adolescents with ASD, relative to controls, in the caudate (McAlonan et al., 2005). With regards to thalamus structure, it has been found that total thalamus volume and grey matter volume in the right thalamus are significantly smaller in children and adolescents with ASD than in their typically developing peers (Tamura et al., 2010). It was also noted that this reduction in total volume was correlated with decreased ability to relate to people as assessed by the Childhood Autistic Rating Scale. These findings tentatively suggest that the structural differences present in the caudate and thalamus may play a part in the symptoms observed in ASD; however, many more studies are needed to support or refute this hypothesis.

The structure of the parietal lobe, an area involved in sensory integration (Blakemore and Sirigu, 2003), has also been investigated in ASD. A whole brain study of 12 Autistic male adolescents observed increased grey matter volume and decreased white matter volume in the parietal lobe of adolescents with ASD compared to typically developing controls (Bonilha et al., 2008). However, a study of 17 medication naïve, Autistic adolescents with no comorbidities found decreased grey matter in parietal lobe (McAlonan et al., 2005).

Mixed findings have also been reported for the structure of the temporal lobe in children with ASD. Increased total volume (Waiter et al., 2004, Jou et al., 2010, Brun et al., 2009), in addition to increased (Bonilha et al., 2008, Waiter et al., 2004) and decreased (Kwon et al 2004) grey matter volume, and decreased white matter volume (Bonilha et al., 2008, Waiter et al., 2005) have all been observed in the temporal lobe of children and adolescents with ASD compared to controls. Whole brain sMRI of

children and adolescents with ASD have also found an increase in total volume of the fusiform gyrus (Waiter et al., 2004), as well as evidence for both increased (Waiter et al., 2004) and reduced (Kwon et al., 2004) grey matter volume in this area.

Structures of the limbic system, which are found in the medial temporal lobe, have long been a point of interest with regards to ASD research due to their role in emotion processing (LeDoux, 2000) and the results from sMRI studies in children with ASD have shown relatively consistent results in these brain regions. Increased total volume of the amygdala, and faster growth, have been reported in young children with ASD compared to healthy controls (Sparks et al., 2002, Schumann et al., 2004, Schumann et al., 2009, Nordahl et al., 2012). Furthermore, this amygdala overgrowth has been shown to be associated with greater social and communication difficulties (Munson et al., 2006, Schumann et al., 2009, Mitchell et al., 2009b), but better joint attention (Mosconi et al., 2009). Increased total volume of the hippocampus and decreased grey matter volume in entorhinal cortex have also been reported in children and adolescents with ASD relative to typically developing children. The increased volume of these structures may lead to increased anxiety and fear during social interactions in individuals with ASD.

In addition to impaired limbic structure, abnormalities of the corpus callosum have also been observed in children with ASD, as reduced volume, thickness and surface area have been reported relative to controls (Waiter et al., 2005, Freitag et al., 2009, Hong et al., 2011). Furthermore, there are consistent findings of decreased fractional anisotropy, which is a measure of how organised and directional the fibres in a tract are, in the corpus callosum of children with ASD compared to controls (Barnea-Goraly et al., 2001, Freitag et al., 2009, Noriuchi et al., 2010, Shukla et al., 2011, Cheon et al., 2011, Wolff et al., 2012, Poustka et al., 2012). There is one study which showed increased fractional anisotropy in young children with ASD (Weinstein et al., 2011). However, this finding may be explained by the low mean age of Weinstein et al's group, which was 3.2 years old, as it has been shown in other neurodevelopmental disorders that increased fractional anisotropy can be indicative of decreased branching (Silk et al., 2009b). Given this, it is likely that increased fractional anisotropy in young children with ASD is due to the decreased branching of the corpus callosal fibres in their immature brain rather than greater fibre organisation

and directionality. A meta-analysis of the abnormalities of the corpus callosum in ASD using 10 studies and a total of 253 children and adults with ASD and 250 controls found decreased total area of the corpus callosum, with the rostral body showing the largest decrease (Frazier and Hardan, 2009). The studies above provide strong evidence for a decrease in the area and fibre organisation in the corpus callosum in children with ASD and suggest that aberrant inter-hemispheric connectivity may play a role in this disorder.

Cortical thickness, on the other hand, produces relatively conflicting findings. In children and adolescents with ASD there is evidence for both increased (Hardan et al., 2006, Hardan et al., 2009, Hyde et al., 2010, Jiao et al., 2010, Mak-Fan et al., 2012) and decreased (Wallace et al., 2010, Hyde et al., 2010, Misaki et al., 2012, Jiao et al., 2010) cortical thickness in frontal, temporal and parietal lobes. These discrepancies may be due to the relatively small sample sizes, heterogeneity of the groups and large age ranges used. This highlights the need for more studies to be conducted in this area in order to elucidate whether there is an increase or decrease in cortical thickness in children and adolescents with ASD compared to controls.

Although there are many caveats of the studies reviewed above, such as small sample size, mixed sex groups, medication use and large age ranges, they provide an intriguing insight into the structural abnormalities observed in children and adolescents with ASD. Findings of increased total cerebral, DLPFC and amygdala volumes have been reliably replicated in children and adolescents with ASD compared to their age matched peers (Sparks et al., 2002, Waiter et al., 2004, Schumann et al., 2004, Schumann et al., 2009, Hazlett et al., 2006, Munson et al., 2006, Brun et al., 2009, Carper and Courchesne, 2005, Mitchell et al., 2009b, Stigler et al., 2011, Nordahl et al., 2012). Furthermore, these abnormalities have been linked to increased Autistic behaviours and are often found in younger children (Munson et al., 2006, Schumann et al., 2009, Mitchell et al., 2009b), suggesting that there is an important link between brain and behaviour that is established during the time when Autistic traits first become prominent (American et al., 1994). There is also evidence to support the presence of a smaller total area of the corpus callosum and decreased fibre organisation, suggesting that connections between the left and right hemisphere are impaired in the brains of Autistic children (Barnea-Goraly et al., 2001, Waiter et

al., 2005, Freitag et al., 2009, Noriuchi et al., 2010, Hong et al., 2011, Shukla et al., 2011, Cheon et al., 2011, Wolff et al., 2012, Poustka et al., 2012). A meta-analysis of the structural abnormalities present in ASD supports these findings as they also found increased volumes in total brain, but they failed to find increased total volumes of DLPFC and amygdala (Stanfield et al., 2008). However, this may be because this meta-analysis included both child and adult studies; it has been shown that the neuroanatomy of the Autistic brain can be very different in childhood, adolescence and adulthood (Courchesne et al., 2001). There is also evidence for decreased cerebellar vermis volumes in children and adolescents with ASD (Courchesne et al., 2001, Brun et al., 2009, Webb et al., 2009), although the findings for total cerebellar volume and parietal and temporal lobe structural abnormalities are quite incongruent and require further investigation in order to disentangle where increased or decreased total, grey and white matter volumes are present.

2.2.3 – Shared and Disorder-Specific Brain Structure Abnormalities in ADHD and ASD

Only two studies have directly compared the neuroanatomy of children with ADHD, children with ASD and typically developing controls. One study found that both patient groups showed a reduction of grey matter volume in left hippocampus-amygdala complex and an increase in grey matter volume in left inferior parietal cortex. They also observed that children with ASD showed a specific increase in right supramarginal gyrus grey matter volume relative to both controls and ADHD, but these findings did not survive correction for multiple testing (Brieber et al., 2007). This may be due to the fact that two of the children in the ASD group were on Risperidone and 10 of the ADHD children were taking methylphenidate (MPH). Furthermore, there was no difference between parent rated ADHD symptoms between the two patient groups which may account for Breiber et al's findings not surviving multiple corrections. The only other to compare boys with ADHD and boys with ASD using sMRI found that with stringent multiple correction testing, ADHD boys showed disorder-specific decreased grey matter of the right posterior cerebellum compared to controls and ASD (Lim et al., 2013), and this is line with the consistent evidence for smaller cerebellar volumes in children with ADHD (Castellanos et al., 2002, Durston et al., 2004, Mackie et al., 2007).

2.3 – White Matter Integrity

2.3.1 – White Matter Integrity in ADHD

The structure and integrity of the tracts between each brain region is as important as the structure of the brain regions themselves as the brain is based on a series of neural networks which work collaboratively to provide information and guide behaviour (Kandel et al., 2000).

A recent neuroimaging technique called diffusion tensor imaging (DTI) investigates the structure of the white matter tracts in the brain by analysing the diffusion of the water molecules in the axons (Basser et al., 1994).

DTI research in children with ADHD has consistently reported decreased fractional anisotropy, indicating impaired white matter integrity, in fronto-striato-cerebellar, fronto-parietal and fronto-limbic areas compared to controls, which is suggestive of delayed white matter maturation (Ashtari et al., 2005, Bechtel et al., 2009, Hamilton et al., 2008, Nagel et al., 2011, Pavuluri et al., 2009, Konrad and Eickhoff, 2010, Liston et al., 2011). A small number of studies have found increased fractional anisotropy in fronto-striatal and parieto-occipital areas in children with ADHD relative to typically developing children (Silk et al., 2009a, Silk et al., 2009b, Davenport et al., 2010, Li et al., 2010, Tamm et al., 2012); this may be indicative of impaired branching of fibres, and therefore evidence of delayed white matter development, in children with ADHD.

Furthermore, a recent meta-analysis supports the findings of decreased white matter integrity in children with ADHD compared to their typically developing peers in right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellar white matter (van Ewijk et al., 2012). This suggests that children with ADHD may have intact branching but poor integrity of important fronto-striato-cerebellar tracts, leading to poor connectivity. This is of particular importance when viewed alongside the structural abnormalities that have been reported in these regions.

2.3.2 – White Matter Integrity in ASD

The theory of long range under-connectivity and short range over-connectivity in ASD was first brought to light in a Positron-Emission Tomography (PET) study by Horwitz et al in 1988 where it was observed that there were different metabolic levels between frontal and posterior regions (Horwitz et al., 1988). It was then formally postulated by Just et al (2004) and Courchesne et al (2005) who, by use of functional connectivity, observed decreased fronto-posterior connectivity in individuals with ASD compared to controls (Just et al., 2005, Courchesne et al., 2005).

As DTI became more popular, studies were conducted in children and adolescents with ASD in order to elucidate whether there were connectivity abnormalities present at a structural level. As was theorised, poor white matter integrity was consistently reported in children with ASD. Decreased fractional anisotropy has been observed in a large number of brain regions and tracts in children and adolescents with ASD compared to controls, namely, frontal lobe, internal and external capsule, superior longitudinal fasciculus and uncinate fasciculus (Barnea-Goraly et al., 2001, Sundaram et al., 2008, Noriuchi et al., 2010, Cheng et al., 2010, Shukla et al., 2011, Cheon et al., 2011, Wolff et al., 2012, Poustka et al., 2012). As the superior longitudinal fasciculus connects the posterior and anterior regions of the brain, consistent findings of its impaired integrity (Barnea-Goraly et al., 2001, Sundaram et al., 2008, Shukla et al., 2011, Poustka et al., 2012) provide compelling structural evidence for this abnormality and complements the metabolic and functional connectivity abnormalities previously reported.

2.4 – Overall Summary of Brain Structure Abnormalities in ADHD and ASD

There are intriguing similarities and differences between the neuroanatomy and developmental trajectory of children with ADHD and children with ASD compared to typically developing children.

One of the most striking potential differences between the two disorders is the way in which their neuroanatomy changes with increasing age. One of the key findings regarding the structural development of children with ADHD is that they have the same trajectory of cortical thickness development as their typically developing peers, but this development appears to be delayed by 2-5 years, in particular in frontal and temporal regions (Shaw et al., 2007). In contrast, one of the key findings regarding the structural development of ASD is that they have an aberrant developmental trajectory that involves a rapid period of brain overgrowth in young childhood followed by a period of decreased growth (Courchesne et al., 2001). However, no study has directly compared the developmental trajectories of these two disorders so at present no conclusions can be drawn about whether they differ in this area.

Furthermore, there appears to be a decrease in total cerebral, frontal and caudate volumes in youths with ADHD compared to controls (Filipek et al., 1997, Overmeyer et al., 2001, Castellanos et al., 2002, Hill et al., 2003, Mostofsky et al., 2002, Sowell et al., 2003a, Durston et al., 2004, Carmona et al., 2005, McAlonan et al., 2007, Wolosin et al., 2009, Batty et al., 2010, Depue et al., 2010a, Nakao et al., 2011, Frodl and Skokauskas, 2012). Conversely, studies in children with ASD have shown an increase in the volume of these areas compared to controls (Sparks et al., 2002, Waiter et al., 2004, Hazlett et al., 2006, Voelbel et al., 2006, Brun et al., 2009, Carper and Courchesne, 2005, Mitchell et al., 2009b, Stigler et al., 2011). However, the only two studies to directly compare between ADHD and ASD found no significant differences in these regions (Brieber et al., 2007, Lim et al., 2013), but disorder-specific decreased right posterior cerebellar grey matter has been reported in children with ADHD compared to both controls and ASD.

There is also some evidence for potential similarities, as both disorders have repeatedly shown that the corpus callosum is reduced in size, area, thickness and fibre organisation in children with ADHD relative to controls (Hill et al., 2003, McAlonan et al., 2007, Luders et al., 2009, Cao et al., 2010, Schnoebelen et al., 2010, Hutchinson et al., 2008), and children with ASD relative to controls (Barnea-Goraly et al., 2001, Waiter et al., 2005, Freitag et al., 2009, Noriuchi et al., 2010, Shukla et al., 2011, Hong et al., 2011, Cheon et al., 2011, Wolff et al., 2012, Poustka et al.,

2012). DTI studies have also found that both disorders show poor white matter integrity in fronto-striatal tracts (Barnea-Goraly et al., 2001, Pavuluri et al., 2009, Cheng et al., 2010, Shukla et al., 2011, Nagel et al., 2011, van Ewijk et al., 2012). This highlights the potentially important role that impaired connectivity plays in both of these disorders, particularly in areas involved in motor response inhibition.

Cortical thickness is an important structure in the brain and although there is evidence to support the presence of thinner frontal cortices and thicker motor and somatosensory cortices in children with ADHD compared to controls (Shaw et al., 2007, Shaw et al., 2006b, Narr et al., 2009, Almeida et al., 2010, Almeida Montes et al., 2012, Duerden et al., 2012), it is extremely difficult to come to a conclusion on whether one would predict similar or different abnormalities in this construct if the two disorders were to be directly compared, due to the inconsistent findings of cortical thickness in children with ASD compared to controls (Hardan et al., 2006, Hardan et al., 2009, Wallace et al., 2010, Hyde et al., 2010, Jiao et al., 2010, Misaki et al., 2012, Mak-Fan et al., 2012)

In conclusion, children with ADHD appear to be characterised by decreased volume in fronto-striatal-cerebellar areas, as well as temporal and parietal lobe, compared to controls (Filipek et al., 1997, Overmeyer et al., 2001, Mostofsky et al., 2002, Castellanos et al., 2002, Hill et al., 2003, Sowell et al., 2003b, Durston et al., 2004, Carmona et al., 2005, McAlonan et al., 2007, Wolosin et al., 2009, Batty et al., 2010, Depue et al., 2010b, Nakao et al., 2011, Frodl and Skokauskas, 2012). Delayed developmental trajectory and reduced levels of cortical thickness in frontal, temporal and parietal lobe have also been reported (Shaw et al., 2006b, Shaw et al., 2007, Narr et al., 2009, Almeida Montes et al., 2012, Almeida et al., 2010, Duerden et al., 2012). In contrast, children with ASD appear to be characterised by a rapid overgrowth of the brain which leads to increased volume in fronto-limbic regions (Sparks et al., 2002, Waiter et al., 2004, Schumann et al., 2004, Schumann et al., 2009, Carper and Courchesne, 2005, Hazlett et al., 2006, Munson et al., 2006, Brun et al., 2009, Mitchell et al., 2009b, Stigler et al., 2011, Nordahl et al., 2012). These potentially differing structural abnormalities are of relevance to this thesis as they may lead to differing functional abnormalities in each disorder.

Chapter 3 - Functional MRI abnormalities in ADHD and ASD

3.1 – Introduction

Functional magnetic resonance imaging (fMRI) is an aspect of neuroimaging which enables researchers to observe the activation of the brain either while the participant is at rest or while he or she performs a particular task in a magnetic resonance imaging scanner (Poldrack et al., 2011).

This method of fMRI neuroimaging first became popular during the 1990's and is based on the fact that when a part of the brain is activated, it needs more oxygen and glucose. The brain seems to overcompensate and send more blood to that area than is necessary for the increased glucose and oxygen extraction of the activated neurons. The net effect of this mechanism is that areas that are activated have more oxygenated blood than areas that are not. This compensatory increase in blood, and its effect on the surrounding tissue, is known as the Blood Oxygenation Level Dependent (BOLD) effect, and this effect is integral for BOLD fMRI (Ogawa et al., 1990, Kim and Ugurbil, 1997). The BOLD effect is based on the magnetic properties of oxyhaemoglobin and deoxyhaemoglobin, as they are isomagnetic and paramagnetic, respectively. Therefore, deoxyhaemoglobin causes a perturbation in the magnetic field induced by the MRI scanner. This perturbation of the magnetic field affects the magnetic resonance of the protons in the water molecules surrounding the deoxyhaemoglobin and this change is detected by the MRI scanner (Turner et al., 1998).

The excellent spatial resolution of both sMRI and fMRI made them popular research tools for psychiatry. This is particularly the case for young, vulnerable patient groups who had been unable to take part in neuroimaging studies that required the injection of radioactive isotopes, such as PET or Single-Photon Emission Computed Tomography (SPECT) studies (Poldrack et al., 2011). These strengths of sMRI and fMRI led to a large increase in their use in children with ADHD and

children with ASD. Given that this PhD focuses on functions of WM, motor response inhibition, and cognitive flexibility, the literature regarding the use of fMRI in children and adolescents in these patient groups in these tasks will be reviewed in detail. Adult studies will only be reported when there is little research in children and adolescents in this field, which applies to fMRI studies of executive functions in ASD. The fMRI literature on other cognitive functions and functional connectivity will also be briefly reviewed.

3.2 – Working Memory

3.2.1 – fMRI of Working Memory in ADHD

As mentioned in Chapter 1 there is strong neuropsychological evidence for a WM deficit in ADHD (Willcutt et al., 2005, Martinussen et al., 2005, Rapport et al., 2008, Kasper et al., 2012) and it has been suggested that this deficit may be the key cognitive impairment in ADHD (Alderson et al., 2010). However, there have been surprisingly few fMRI studies focused on uncovering the neural correlates of this WM impairment in children and adolescents with ADHD.

In healthy children and adolescents fronto-parietal networks are activated during tasks of WM and it has been reported that activation in these areas increases with high WM loads (Casey et al., 1995, Klingberg et al., 2002, Luna et al., 2010).

Two whole brain fMRI studies focusing on spatial WM during a task of mental rotation found decreased activation in a group of seven, and a group of 12, medication naïve children with ADHD in areas such as bilateral IFC, left superior frontal cortex, caudate, right superior/inferior parietal lobe, right superior temporal lobe and right occipital lobe compared to controls. (Silk et al., 2005, Vance et al., 2007). Increased activation was also observed in default mode network (DMN) areas such as PCC and mPFC, as well as middle and superior temporal gyri (Silk et al., 2005). Silk et al also noted that children with ADHD were significantly less accurate in their task performance.

The DMN consists of a number of functionally connected, medially located brain regions, including mPFC, PCC, precuneus, inferior temporal lobe and inferior parietal lobe (Raichle et al., 2001, Sonuga-Barke and Castellanos, 2007, Northoff et al., 2010). These brain regions show spontaneous, low frequency ($<0.1\text{Hz}$) activation during rest (Greicius et al., 2003, Fox et al., 2005, Sonuga-Barke and Castellanos, 2007, Northoff et al., 2010) and this DMN activation has been associated with stimulus independent, self-referential thought (Mason et al., 2007, Sonuga-Barke and Castellanos, 2007). It has been consistently reported that activation of this DMN is anti-correlated with brain regions involved in the performance of the task, indicating that when task positive networks are active, the task-negative DMN is deactivated (Greicius et al., 2003, Fox et al., 2005, Northoff et al., 2010). This occurs to enable effective completion of the task at hand and if there is poor deactivation of the DMN, a competition occurs between goal-directed behaviour and stimulus independent thoughts, leading to poor performance and attention lapses, presumably due to “mind wandering” (Sonuga-Barke and Castellanos, 2007, Northoff et al., 2010). Furthermore, it has been observed that the functional connectivity of the DMN increases with age, as does the ability to deactivate it during goal-directed performance (Power et al., 2010). Therefore, findings of poor deactivation in DMN areas in children with ADHD during a WM task is likely to reflect abnormalities with switching off task-irrelevant thinking (Silk et al., 2005).

Two whole-brain fMRI studies using a delayed match to sample task reported decreased activation in right IFC, ACC and bilateral caudate during encoding and retrieval of information in a group of 10 girls, and a group of 12 boys, with ADHD compared to their typically developing peers (Sheridan et al., 2007, Prehn-Kristensen et al., 2011). Sheridan et al then investigated the correlation between reaction time and three ROIs in left ventrolateral prefrontal cortex (VLPFC), left DLPFC and primary motor cortex. It was observed that there was a significant correlation between faster information retrieval and increased VLPFC activation in the ADHD group and this correlation pattern was also evident in, but not significant for, DLPFC. Nonetheless, ADHD group RT-ROI correlations in VLPFC and DLPFC were significantly different from that of the control group where faster retrieval was correlated with decreased activation in these areas (Sheridan et al., 2007). Both studies used participants with a history of stimulant medication and Prehn-Kristensen

et al observed that after a 48hr washout period the ADHD group were significantly less accurate in their responses compared to controls.

A visual serial addition task which tapped into WM processes found increased activation compared to controls in a group of 12 medicated adolescent ADHD participants after a 48 hour washout period in mPFC when using mPFC, PCC, precuneus and ACC as ROIs. No behavioural differences were reported between the two groups, however, it was observed that reaction time variability was positively correlated with ventromedial prefrontal cortex (vmPFC) activation and negatively correlated with superior mPFC activation in the ADHD group alone (Fassbender et al., 2009). Another study by the same group using the same paradigm and mainly the same participants showed increased activation in right IFC, insula and right putamen in 13 children with ADHD compared to controls in a whole brain analysis. However, an ROI analysis using inferior and middle frontal cortices showed decreased activation in ADHD subjects in left middle frontal cortex compared to controls. The only significant behavioural difference observed was that the ADHD group made more omission errors on the visual serial addition task than controls (Fassbender et al., 2011). Only one study in 14 children with ADHD used the classic verbal N-Back task and they observed that after a 24hr medication washout the ADHD children showed decreased activation in left precentral cortex, bilateral parietal lobe and right cerebellum compared to controls (Kobel et al., 2009). It was also noted that the ADHD group performed significantly worse on the 2-Back and 3-Back conditions compared to typically developing children (Kobel et al., 2009).

There are large differences in the tasks and subject groups in each of these studies. Many used different WM paradigms which elicit activation in different brain regions; as it is known, for example, that spatial WM involves more right hemispheric brain regions and verbal WM more left hemispheric brain regions (D'Esposito et al., 1998). In addition, the inclusion of mixed gender groups, co-morbidities and small sample sizes are all caveats when investigating neurofunctional abnormalities in ADHD during tasks of WM. The problems of including mixed gender groups in ADHD during a task of WM has been highlighted in an fMRI study on WM in a group of 44 adults with ADHD, of which 21 were female. It was noted that the inclusion of females with ADHD, who showed no deficits relative to female controls,

overshadowed the differences observed in males alone in fronto-striato-cerebellar regions, which are key regions of dysfunction in ADHD. This highlights how crucial it is that single sex groups are tested in fMRI studies in order to increase homogeneity and understand brain differences according to gender (Valera et al., 2010). Nonetheless, taking these caveats into account, it can be concluded that during tasks of WM, children and adolescents with ADHD have decreased activation in vital areas for WM such as right IFC, bilateral caudate and bilateral parietal lobe as well as decreased deactivation in the DMN, in particular mPFC, both of which may play a role in the poor task performance observed in some of the studies (Vance et al., 2007, Silk et al., 2005, Sheridan et al., 2007, Prehn-Kristensen et al., 2011, Kobel et al., 2009, Fassbender et al., 2009, Fassbender et al., 2011).

3.2.2 – fMRI of Working Memory in ASD

Although the evidence for WM deficits in ASD is not as robust as those for ADHD, it has been reported that individuals with ASD have impaired WM (Williams et al., 2005, Steele et al., 2007, Geurts and Vissers, 2012). Despite these neuropsychological findings only one study has investigated the neural correlates of WM in children with ASD using fMRI (Silk et al., 2006). This whole brain fMRI study used the same mental rotation task that was used in children with ADHD to assess spatial WM (Silk et al., 2005, Vance et al., 2007). In seven children who met the DSM-IV criteria for Autistic Disorder or Asperger's a significant decrease in activation was reported in right IFC, right mPFC, ACC and right caudate, while decreased activation in left DLPFC was just below significance, compared to controls.

However, a small number of ROI fMRI studies in adults have attempted to uncover the neurofunctional underpinnings of the WM deficit in ASD (Luna et al., 2002, Koshino et al., 2005, Koshino et al., 2008). Studies using a variation of the N-Back task found decreased activation in a group of 14 High Functioning Autistics (HFA), and a group of 11 Autistic subjects, compared to controls in left DLPFC, left inferior/middle frontal cortex, left inferior parietal lobe and right superior/middle temporal lobe. It was also observed that individuals with ASD had increased activation in right superior/inferior frontal cortex, right superior/inferior parietal lobe,

left inferior temporal and left occipital lobe (Koshino et al., 2005, Koshino et al., 2008).

An ROI study using a delayed match to sample task, where subjects had to remember the location of a brief stimulus to the left or right of the centre of the screen (at 9, 18 or 27 degrees) and shift their gaze to the remembered location after a delay period of 1, 2, 4 or 8 seconds, observed decreased activation in right DLPFC and PCC in 11 Autistic adults compared to healthy adults (Luna et al., 2002). Autistic individuals were significantly less accurate in their eye movements compared to controls outside of the scanner. However, there was no scanner performance data, as eye tracking could not be performed in the scanner, and this is a large caveat of this study (Luna et al., 2002, Rajah and D'Esposito, 2005).

As the majority of these studies used adults, only tentative hypotheses can be drawn about how many of these deficits would be present in the child and adolescent ASD population, as it has been previously shown that brain activation in children and adults differ in tasks of WM (Rajah and D'Esposito, 2005, Luna et al., 2010). Furthermore, the small number of studies in this field, the heterogeneity of the participants and the fact that most of the adult studies used ROI analyses (Luna et al., 2002, Koshino et al., 2005) may lead to unclear and slightly biased results.

However, after acknowledging these limitations it can be concluded that children with ASD have been shown to have decreased activation in right fronto-striatal regions during tasks of spatial WM (Silk et al., 2006). Adults with ASD show decreased activation during verbal WM tasks in mainly left hemispheric areas such as left inferior/middle frontal cortex and inferior parietal lobe, as well as bilateral DLPFC, but exhibit increased activation in mainly right hemispheric areas such as right superior/inferior frontal cortex and right superior/inferior parietal lobe (Luna et al., 2002, Koshino et al., 2005, Koshino et al., 2008).

3.2.3 – Summary of fMRI of Working Memory in ADHD and ASD

Although there is limited fMRI knowledge of WM in both ADHD and ASD the studies reviewed above are still able to shed light on the potential neurofunctional abnormalities underlying the cognitive deficit in this domain in these disorders

Both children with ADHD (Silk et al., 2005, Vance et al., 2007, Kobel et al., 2009, Fassbender et al., 2011, Prehn-Kristensen et al., 2011), and children with ASD (Silk et al., 2006), have shown abnormal activation compared to controls in IFC, ACC and caudate during WM tasks.

Abnormalities have also been reported in mPFC, with children with ADHD showing increased activation (Silk et al., 2005, Fassbender et al., 2009), and children with ASD showing decreased activation (Silk et al., 2006), during tasks of WM compared to controls.

Decreased activation in parietal lobes and increased activation in PCC while performing tasks of WM has been reported in children with ADHD compared to typically developing youths (Silk et al., 2005, Vance et al., 2007, Kobel et al., 2009). However, there are too few studies in WM in children with ASD to discern whether this deficit is present in this patient group.

Adults with ASD show a slightly different pattern of abnormalities during verbal WM tasks, with decreased left fronto-parietal activation, and increased right fronto-parietal activation, being reported (Koshino et al., 2005, Koshino et al., 2008). It has been hypothesised that this increase in right hemispheric activation may be due to the adult ASD group viewing the verbal and facial N-Back stimuli as an object and therefore using less phonetic strategies, which would require less left brain activation, to view and encode the information (Koshino et al., 2005, Koshino et al., 2008). This has been supported by the differences in the laterality of the WM deficits during tasks of verbal WM in adults with ASD and spatial WM in children with ASD (Silk et al., 2006). However, this needs to be corroborated by studies including verbal and spatial WM tasks in children or adults alone.

In summary, during WM there is evidence that children with ADHD (Vance et al., 2007, Silk et al., 2005, Sheridan et al., 2007, Prehn-Kristensen et al., 2011, Kobel et al., 2009, Fassbender et al., 2009, Fassbender et al., 2011) and children ASD (Silk et al., 2006) both have abnormal activation in a right hemispheric network involving important areas for WM such as IFC, mPFC, ACC and caudate. However it is not known whether these deficits are shared between the disorders.

Adults with ASD have increased right hemispheric activation and it has been speculated that this increased activation may be compensation for the more left hemispheric deficits in inferior frontal cortices and parietal lobe during tasks of verbal WM (Koshino et al., 2005, Koshino et al., 2008).

It is not possible to compare childhood and adult fMRI data due to the large differences in brain activation between children and adults during WM tasks (Rajah and D'Esposito, 2005, Luna et al., 2010). Therefore little can be said about potential differences and similarities in brain activation during WM given that there is only one fMRI study in children with ASD that assesses WM.

3.3 – Motor and Interference Inhibition

3.3.1 – fMRI of Motor Response Inhibition in ADHD

Given the consistent evidence for deficits in motor response inhibition in ADHD (Oosterlaan et al., 1998, Rubia et al., 2001b, Rubia et al., 2007a, Nigg and Casey, 2005, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Adams et al., 2008), a large amount of fMRI research has been conducted in order to discern whether there are neurofunctional abnormalities in the inhibitory network in the brains of children with ADHD.

In healthy adolescents and adults performing tasks of motor response inhibition activation has most consistently been observed in IFC, supplementary motor area (SMA), ACC, subthalamic nucleus and caudate (Rubia et al., 2001a, Rubia et al., 2003, Rubia et al., 2006, Rubia et al., 2007c, Aron and Poldrack, 2006, Chevrier et al.,

2007, Simmonds et al., 2008, Chambers et al., 2009). Furthermore, linear, developmentally induced changes in neurofunctional activity during motor response inhibition have been reported. Increased activity in right IFC, ACC, OFC and caudate were observed in a linear pattern in healthy adults compared to healthy adolescents during successful motor response inhibition and this increased activity was related to better task performance. These findings suggest that there is a ‘frontalisation’ of neurofunctional activity during typical development which leads to better motor response inhibition with increasing age (Rubia et al., 2007c, Rubia et al., 2006, Bunge et al., 2002, Bunge and Wright, 2007).

Both whole brain and ROI studies focusing on the Go/No-Go task in children and adolescents with ADHD found relatively consistent results (Durstan et al., 2003, Durston et al., 2006, Schulz et al., 2004, Booth et al., 2005, Smith et al., 2006, Epstein et al., 2007, Suskauer et al., 2008, Mulder et al., 2008). Most studies found that children with ADHD exhibited decreased activation in task relevant frontal regions, such as ACC, SMA and inferior/middle/superior frontal cortex and key subcortical and posterior areas such as the caudate, putamen, thalamus and cerebellum, when compared to their typically developing peers (Schulz et al., 2004, Tamm et al., 2004, Booth et al., 2005, Durston et al., 2006, Smith et al., 2006, Epstein et al., 2007, Suskauer et al., 2008, Mulder et al., 2008). However, a minority of studies, using mainly ROI analyses, also provided evidence for increased activation in middle/superior frontal cortex and ACC during successful inhibition in children and adolescents with ADHD when compared to healthy controls (Durstan et al., 2003, Schulz et al., 2004). However, the ADHD group in Schulz et al’s study had an upper age limit of 20 years old and a mean group age of 18, so their patterns of brain activation may be more akin to that of adults with ADHD. Furthermore, Durston et al used a small sample size of seven medicated ADHD children of mixed sex and subtype. Thus, the age of the participants in Schulz et al, and the heterogeneity of the participants in Durston et al, may account for their findings of increased activation in middle/superior frontal cortex and ACC which are contrary to the findings of decreased activation in these areas in the majority of studies (Tamm et al., 2004, Booth et al., 2005, Durston et al., 2006, Epstein et al., 2007, Suskauer et al., 2008).

There is also evidence for abnormal functioning of the temporal and parietal lobe in children and adolescents with ADHD during successful motor response inhibition in a Go/No-Go task (Durstion et al., 2003, Durstion et al., 2006, Tamm et al., 2004, Schulz et al., 2004, Epstein et al., 2007, Suskauer et al., 2008). Studies have found increased activation in children with ADHD compared to controls in left inferior/middle temporal lobe and bilateral superior temporal lobe (Durstion et al., 2003, Tamm et al., 2004). However, other studies have found decreased activation in right inferior temporal lobe and the right temporo-parietal junction (Schulz et al., 2004, Suskauer et al., 2008). Both increased (Schulz et al., 2004, Durstion et al., 2003), and decreased activation (Durstion et al., 2006, Epstein et al., 2007) have been reported in bilateral inferior parietal lobe in children with ADHD compared to healthy children during a Go/No-Go task, making it difficult to hypothesise the direction of the brain dysfunction in these areas during this task. However, as temporal and parietal lobes are involved in visual-spatial attention (Colby and Goldberg, 1999, Rubia et al., 2007b, Zhang et al., 2009, Bisley and Goldberg, 2010) one can speculate that the abnormalities observed in these regions are due to the attentional demands of the task.

Other areas that have shown altered neurofunctional ability during successful inhibition in a Go/No-Go task performed by children with ADHD compared to controls are rostral mPFC, precentral gyrus and occipital lobe (Durstion et al., 2003, Tamm et al., 2004, Schulz et al., 2004, Booth et al., 2005, Smith et al., 2006, Suskauer et al., 2008, Mulder et al., 2008).

As mentioned in Chapter 1, another classic paradigm for testing motor response inhibition is the Stop Signal task. Whereas the aforementioned Go/No-Go task requires the participant to either make or inhibit a response, the Stop Signal task requires the participant to inhibit a response that has already been triggered and is in the process of being made. Consequently, the inhibitory load present in the Stop Signal task is much higher than that of the Go/No-Go task, making the Stop Signal task a more focused paradigm for investigating motor response inhibition. For this reason, this task has been used in numerous fMRI studies to elucidate the neurofunctional underpinnings of the inhibitory impairment in ADHD (Rubia et al.,

1999, Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2010b, Rubia et al., 2011c, Pliszka et al., 2006).

The majority of fMRI studies that have used the Stop Signal task have used children who are medication naïve, all diagnosed with the combined subtype of ADHD, all male, all right handed and who had no comorbidities apart from oppositional defiance disorder/conduct disorder (Rubia et al., 1999, Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2010b, Rubia et al., 2011c). These studies also used whole brain fMRI analyses. Consequently, it is not surprising that the use of these homogeneous groups in a challenging task of motor response inhibition has produced more consistent results than those using the Go/No-Go task (Schulz et al., 2004, Booth et al., 2005, Durston et al., 2006, Epstein et al., 2007).

During successful inhibition decreased activation has consistently been observed in children with ADHD compared to their typically developing peers in frontal-striatal brain regions, most prominently in the right IFC, right OFC, right mPFC, left DLPFC, bilateral caudate, thalamus and putamen (Rubia et al., 1999, Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2010b, Rubia et al., 2011c). In some of these studies children with ADHD also showed increased activation, alongside reduced activation, during successful inhibition in a small cluster in SMA (Rubia et al., 1999) ACC and right DLPFC, when compared to controls (Pliszka et al., 2006).

When combining the fMRI findings from the Go/No-Go task and the Stop Signal task in children with ADHD there is consistent evidence for reduced activation in right inferior/middle/superior frontal cortices, right OFC, mPFC, bilateral striatum and bilateral thalamus during successful inhibition compared to controls (Rubia et al., 1999, Rubia et al., 2005b, Rubia et al., 2010b, Rubia et al., 2011c, Tamm et al., 2004, Booth et al., 2005, Durston et al., 2006, Smith et al., 2006, Epstein et al., 2007). These findings have been corroborated by two meta-analyses (Dickstein et al., 2006, Hart et al., 2013). Dickstein et al used 16 studies in their meta-analysis and when focusing on response inhibition decreased activation was observed in IFC, left parietal lobe, right caudate and bilateral ACC of individuals with ADHD compared to controls. Increased activation in ADHD patients was observed in medial frontal gyrus and left paracentral gyrus relative to controls. Hart et al's is the most recent meta-analysis of fMRI

inhibition studies in ADHD, including 15 studies and a total of 187 individuals with ADHD and 206 controls, when focusing on motor response inhibition. The results were very similar to those reported by Dickstein et al, as consistently decreased activation across studies was observed in individuals with ADHD in right IFC, SMA/ACC, right thalamus and left caudate compared to controls. This suggests that there is consistent evidence for inferior and medial fronto-striato-thalamic deficits in children with ADHD during successful inhibition (Dickstein et al., 2006, Cortese, 2012, Hart et al., 2013).

Failed inhibition is when a subject makes an incorrect go response at any point during the stop trial. The subsequent stop signal then acts as feedback, informing the participant of their error. The brain activation observed during failed inhibition can enhance our knowledge of the neurofunctional underpinnings of error detection and performance monitoring. Activation in IFC, ACC, PCC and temporo-parietal regions have been consistently reported in healthy children and adults during motor inhibition failures and are considered part of an error detection and performance monitoring network (Rubia et al., 2003, Rubia et al., 2007c, Rubia, 2012, Li et al., 2006, Chevrier et al., 2007). Furthermore, frontal parts of this network such as IFC and ACC have been shown to increase in activation in a linear manner with increasing age (Rubia et al., 2007c, Velanova et al., 2008).

Some studies have measured error detection in the Go/No-Go task. However, in ADHD our knowledge of the neurofunctional abnormalities in failed inhibition are based mainly on findings from the tracking Stop Signal task. This is because the tracking algorithm of the stop signal task ensures that participants fail to inhibit their response 50% of the time. Therefore there are a high number of failed inhibition trials to analyse, as well as an equal number of successful and unsuccessful trials to compare and contrast against each other (Logan et al., 1997).

These studies show that deficits in inferior and medial fronto-striatal, but also thalamic, regions such as right middle/inferior frontal cortex, ACC, striatum and bilateral subthalamic nuclei are also present during failed inhibition (Rubia et al., 2010a, Rubia et al., 2011c, Pliszka et al., 2006). However, as opposed to the evidence for deficits during successful trials, there is additional evidence for more posterior

deficits in right PCC, precuneus, and cerebellum, presumably mediating visual-spatial attention to saliency, given that errors are highly salient stimuli (Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2011c). Thus, in addition to exhibiting decreased activation in key areas of inhibition, children with ADHD also exhibit decreased activation in performance monitoring networks when they fail to inhibit.

In addition to these neurofunctional abnormalities, and despite the relatively small numbers of fMRI studies and hence reduced power for neuropsychological data analyses, several fMRI studies have shown that individuals with ADHD perform worse on these tasks as they make more commission and omission errors, have larger reaction time variability and longer SSRTs (Durstun et al., 2003, Rubia et al., 2005b, Rubia et al., 1999, Rubia et al., 2008, Rubia et al., 2011c, Durston et al., 2006, Tamm et al., 2004, Schulz et al., 2004, Booth et al., 2005, Pliszka et al., 2006, Smith et al., 2006, Epstein et al., 2007, Suskauer et al., 2008, Mulder et al., 2008). However, most fMRI studies report no differences in performance between groups due to the relatively small sample size of groups in fMRI studies. A sample size with approximately 20 in each group has been shown to provide adequate power in fMRI studies (Thirion et al., 2007) compared to neuropsychological studies which typically require larger sample sizes for adequate power.

In order to gain further knowledge on the link between brain dysfunction and performance, many studies correlated brain activation with performance measures. From these investigations it was noted that in ADHD children increased activation in right IFC and right parietal lobe during successful motor response inhibition was linked to better accuracy and ability to distinguish targets from non-targets, respectively (Durstun et al., 2006, Epstein et al., 2007). It was also observed that in the ADHD group increased post-error slowing in the Stop Signal task was correlated with increased PCC activation during successful inhibition and activation in a performance monitoring network of left IFC and dorsomedial prefrontal cortex (dmPFC) during failed inhibition (Rubia et al., 2011c). Furthermore, correlations of brain activation and ADHD symptoms have shown that higher scores on the hyperactive/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ) were correlated with lower activation in right IFC and PCC during successful and failed inhibition, respectively (Rubia et al., 2005b).

As previously mentioned the use of small sample sizes, subjects with psychiatric comorbidities, large age ranges, mixed sex groups, history of previous medication and mixed subtypes are all caveats of the studies above, particularly those who used the Go/No-Go task (Durstun et al., 2003, Schulz et al., 2004, Pliszka et al., 2006, Suskauer et al., 2008, Mulder et al., 2008).

Despite these limitations some consistent brain abnormalities have been found when combining all studies that have investigated motor inhibition in children in ADHD. In conclusion, children with ADHD have deficits in a right lateralised fronto-striatal-thalamic inhibition network during both successful and unsuccessful inhibition. However, these deficits extend into more posterior regions such as right PCC and right precuneus during unsuccessful inhibition (Rubia et al., 1999, Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2010a, Rubia et al., 2011c, Tamm et al., 2004, Booth et al., 2005, Durstun et al., 2006, Smith et al., 2006, Epstein et al., 2007, Hart et al., 2013).

3.3.2 – fMRI of Interference Inhibition in ADHD

Another form of inhibition is interference inhibition, which requires the suppression of a predominant response in order for the subject to respond to a conflicting, non-dominant response. It can be assessed using a number of tasks, the most popular of which are the Stroop, the Simon and the Flanker task (Golden, 1978, Simon, 1990, Eriksen and Schultz, 1979).

Studies in healthy adults and children have found that the inhibition of a prepotent dominant response, and the execution of a less dominant conflicting response, activates DLPFC, IFC, ACC posterior parietal lobe and anterior insula (Rubia et al., 2006, Christakou et al., 2009b, Derrfuss et al., 2005, Chevrier et al., 2007, Nee et al., 2007). However, the pattern of brain activation elicited during interference inhibition differs with age as a linear increase in activation is observed in inferior frontal and temporo-parietal brain regions in healthy adults when compared to

typically developing children and adolescents (Adleman et al., 2002, Rubia et al., 2006, Marsh et al., 2006, Wood et al., 2009, Christakou et al., 2009b).

Findings of interference inhibition deficits have not always been consistent in ADHD (Homack and Riccio, 2004, Van Mourik et al., 2005, Lansbergen et al., 2007, Schwartz and Verhaeghen, 2008, Mullane et al., 2009). A number of studies, many of which have used medication naïve patient groups and whole brain fMRI analysis (Konrad et al., 2006, Smith et al., 2006, Rubia et al., 2009c, Rubia et al., 2011b, Rubia et al., 2011a), have researched the neural correlates of interference inhibition in children with ADHD using fMRI (Schulz et al., 2005, Vaidya et al., 2005, Konrad et al., 2006, Rubia et al., 2009c, Rubia et al., 2011b, Rubia et al., 2011a, Vloet et al., 2010).

Focusing on brain activation during conflict trials in a Simon task, a spatial stimulus response task and a modified Flanker task, it has been observed that ADHD children show decreased activation in right SMA and ACC, left mPFC, left precentral gyrus, bilateral putamen, right inferior/superior parietal lobe and bilateral middle/superior temporal lobe, relative to typically developing children (Konrad et al., 2006, Rubia et al., 2009c, Rubia et al., 2011b, Rubia et al., 2011a, Vloet et al., 2010). However, there have also been findings of no deficits (Smith et al., 2006). Both decreased (Vaidya et al., 2005, Rubia et al., 2011b) and increased (Schulz et al., 2005) activation have been observed in bilateral IFC in children with ADHD during conflict trials compared to controls; however, the study reporting increased activation in this area has more limitations than those reporting decreased activation. The patient group in Schulz et al's study consisted of only eight ADHD patients of mixed handedness, four of which are described as being in remission. Thus, the larger patient numbers and superior diagnostic criteria in Vaidya et al and Rubia et al's studies make the relatively reproducible finding of decreased IFC activation in children with ADHD during interference inhibition more reliable than that of decreased activation (Vaidya et al., 2005, Rubia et al., 2011b).

When focusing on six studies of interference inhibition, a recent meta-analysis including 100 ADHD patients and 114 controls found consistently decreased activation in ADHD individuals in left ACC, insula and parietal lobe and right

IFC/insula and caudate compared to controls (Hart et al., 2013). Compared to the motor inhibition findings from this meta-analysis, the neurofunctional abnormalities during interference inhibition in ADHD were more left hemispheric and did not involve the key areas for motor response inhibition, such as the SMA and thalamus.

The performance data from these studies suggest that children with ADHD are impaired in behavioural measures of interference inhibition as it has been shown that they make significantly more errors and are less accurate in their responses than typically developing children (Konrad et al., 2006, Vaidya et al., 2005, Vloet et al., 2010).

Correlating behaviour and brain activation during interference inhibition has shown that, in children with ADHD, an increased number of symptoms correlates with decreased activation in the basal ganglia and increased activation in left IFC (Schulz et al., 2005, Konrad et al., 2006, Rubia et al., 2011b), whereas better interference suppression is correlated with increased activation in left IFC, thalamus and middle temporal lobe (Vaidya et al., 2005).

To conclude; during tasks of interference inhibition, children with ADHD show activation deficits in IFC, right SMA/ACC, bilateral putamen and temporo-parietal regions compared to healthy controls (Schulz et al., 2005, Vaidya et al., 2005, Konrad et al., 2006, Rubia et al., 2009c, Rubia et al., 2011a, Rubia et al., 2011b, Vloet et al., 2010), with the left IFC, ACC and striatum being the most consistent areas of deficit across studies (Hart et al., 2013).

3.3.3 – fMRI of Motor Response and Interference Inhibition in ASD

While there is evidence for motor response inhibition deficits in individuals with ASD (Christ et al., 2007, Hill, 2004, Sanders et al., 2008, O'Hearn et al., 2008, Rommelse et al., 2011), and slightly more mixed evidence for interference inhibition deficits (Hill, 2004, Christ et al., 2007, Christ et al., 2011, Solomon et al., 2008, Adams and Jarrold, 2009, Robinson et al., 2009), only three studies have used fMRI

to uncover the neurofunctional basis of this executive dysfunction in individuals with ASD.

Thus far, no study has tested the neurofunctional deficits of motor response inhibition in ASD children. However, one ROI study has tested interference inhibition in 22 children with HFA/Asperger's using a Preparing to Overcome Prepotency task, which is similar to a Simon task. While children with ASD performed this task, decreased activation was observed in bilateral middle/superior frontal cortex, bilateral superior parietal lobe, bilateral precuneus, left inferior parietal lobe and left premotor cortex, compared to controls. It was also observed that the patient group made significantly more errors than the control group on the incongruent trials. (Solomon et al., 2009).

In adults with ASD, two whole brain fMRI studies have investigated motor response inhibition (Kana et al., 2007, Schmitz et al., 2006). During successful inhibition in a Go/No-Go task, 12 adults with HFA showed decreased activation in right insula, right IFC, right ACC and right premotor cortex compared to healthy controls (Kana et al., 2007). However, another study found that 10 adults with Asperger's syndrome showed increased activation during optimal task performance in left IFC and OFC compared to their typically developing peers (Schmitz et al., 2006).

The strengths of the studies mentioned above are that they were conducted on ASD individuals who were diagnosed using gold standard diagnostic tools, such as the ADI and the ADOS and that the participants had no comorbidities (Kana et al., 2007, Schmitz et al., 2006, Solomon et al., 2009). However, most studies involved small patient groups with mixed sex and handedness and a number of the participants were on medication (Schmitz et al., 2006, Kana et al., 2007, Solomon et al., 2009). These limitations may explain the different results obtained by Kana et al compared to Schmitz et al (Kana et al., 2007, Schmitz et al., 2006). However, results from the child study of interference inhibition support the findings of decreased activation during inhibitory processes in individuals with ASD, particularly in frontal areas (Solomon et al., 2009).

These caveats limit the reliability of the results obtained from these studies, but it has been observed that during successful motor response and interference inhibition children and adults with ASD show decreased activation in ACC, right IFC, bilateral superior/middle cortex and bilateral premotor cortex (Solomon et al., 2009, Kana et al., 2007). Increased activation in left IFC and left OFC has also been observed in adults with Asperger's (Schmitz et al., 2006). However, the inconsistency of these findings in the adult literature highlights the need for further studies in this field.

3.3.4 – Summary of fMRI of Inhibition in ADHD and ASD

One of the most consistent deficits in ADHD is that of motor response inhibition (Oosterlaan et al., 1998, Nigg and Casey, 2005, Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Adams et al., 2008); consequently, a large proportion of ADHD fMRI research has focused on uncovering the neural correlates of this deficit. There is a large body of fMRI research investigating the brain dysfunction of children with ADHD during tasks of inhibitory control (Durstun et al., 2003, Durston et al., 2006, Tamm et al., 2004, Booth et al., 2005, Schulz et al., 2005, Vaidya et al., 2005, Konrad et al., 2006, Smith et al., 2006, Epstein et al., 2007, Suskauer et al., 2008, Mulder et al., 2008, Rubia et al., 1999, Rubia et al., 2005b, Rubia et al., 2008, Rubia et al., 2009c, Rubia et al., 2010a, Rubia et al., 2011c, Rubia et al., 2011b, Rubia et al., 2011a, Vloet et al., 2010). Despite the evidence for motor response and interference inhibition deficits in ASD (Hill, 2004, Christ et al., 2007, Christ et al., 2011, Solomon et al., 2008, Sanders et al., 2008, Robinson et al., 2009, Rommelse et al., 2011), surprisingly few studies have researched the underlying neurofunctional abnormalities of these impairments (Schmitz et al., 2006, Kana et al., 2007, Solomon et al., 2009). The studies that have investigated inhibition in ASD have used adults, apart from one study researching interference inhibition in children. (Solomon et al., 2009). It is therefore difficult to hypothesise potential differences or similarities in brain activation deficits between the two disorders.

Nonetheless, it has been observed that there is a right lateralised fronto-striatal and temporo-parietal deficit in children with ADHD during successful motor response inhibition compared to controls (Rubia et al., 1999, Rubia et al., 2008, Rubia

et al., 2011c, Tamm et al., 2004, Booth et al., 2005, Vaidya et al., 2005). This has been confirmed in two meta-analyses which found predominately right hemispheric deficits in IFC, ACC/SMA and caudate/thalamus (Dickstein et al., 2006, Hart et al., 2013). Children with ASD have also been shown to exhibit middle/superior fronto-parietal deficits (Solomon et al., 2009). However, as these deficits are observed in only one study focusing on interference inhibition it is difficult to compare these findings to the wealth of fMRI literature on inhibition in children with ADHD.

Adults with ASD appear to exhibit a similar pattern of dysfunction as children with ADHD when compared to their typically developing peers, as they too have decreased right frontal activation during motor response inhibition (Kana et al., 2007). This decreased activation is observed particularly in right ACC and right inferior/middle frontal cortex (Kana et al., 2007, Solomon et al., 2009), which has also been observed in children with ADHD (Rubia et al., 1999, Booth et al., 2005, Epstein et al., 2007, Hart et al., 2013).

However, ASD individuals have been shown to have left lateralised frontal abnormalities during successful inhibition, as an increase in activation in left IFC and left OFC has been reported in adults with ASD, and a decrease in activation in left premotor cortex and left parietal lobe in children with ASD compared to age matched controls during Go/No-Go and Preparing to Overcome Prepotency tasks, respectively. (Schmitz et al., 2006, Solomon et al., 2009).

Adolescents with ADHD have also been shown to have consistent deficits in striatal activation during successful inhibition (Rubia et al., 1999, Rubia et al., 2005b, Durston et al., 2003, Booth et al., 2005, Epstein et al., 2007), which has so far not been reported to be abnormal in adults with ASD during successful inhibition in Go/No-Go tasks (Kana et al., 2007, Schmitz et al., 2006). However, there is only one study in children with ASD and so few studies in adults with ASD that hypothesising potential differences or similarities in brain abnormalities is not possible.

As previously mentioned, the heterogeneity of the individual studies investigating the neural correlates of inhibition in ADHD and ASD, the wealth of research in this field in children with ADHD compared to individuals with ASD and

the difficulties in comparing adult and child studies mean that one cannot convincingly postulate about potential similarities and differences. While there is consistent evidence for ADHD children to have reduced frontal and striato-thalamic deficits during motor and interference inhibition, there is some preliminary evidence that children with ASD and adults with ASD also have abnormalities in frontal areas, but more in the left hemisphere (Schmitz et al., 2006, Solomon et al., 2009), while striato-thalamic deficits have not been observed.

3.4 – Cognitive Flexibility

3.4.1 – fMRI of Cognitive Flexibility in ADHD

As mentioned in Chapter 1, cognitive flexibility is the ability of a person to make stimulus-response associations and adapt them based on feedback (Milner, 1963) and this executive function can be assessed using tasks such as the WCST, Meiran Switch task and reversal learning tasks such as the ID/ED task of the CANTAB (Milner, 1963, Meiran, 1996, Robbins et al., 1994).

During switching tasks, healthy children and adults activate IFC, DLPFC, ACC and parietal lobe (Derrfuss et al., 2005, Rubia et al., 2006, Loose et al., 2006, Ravizza and Carter, 2008, Christakou et al., 2009b). Developmental differences have also been observed during switching tasks, as it has been reported that healthy adults activate IFC, ACC, DLPFC, parietal lobe and basal ganglia more than typically developing children, and there is evidence for linear activation increase between childhood and adulthood (Casey et al., 2004, Rubia et al., 2006, Christakou et al., 2009b).

However, in healthy adults, reward reversal learning recruits a slightly different, more medial network of brain regions, including mPFC, medial OFC and ACC, as well as VLPFC, and the striatum (O'Doherty et al., 2001, O'Doherty et al., 2003, Cools et al., 2002, Remijnse et al., 2005, Cohen et al., 2008, Kehagia et al., 2010). Only one ROI study has investigated the developmental trajectory of reversal learning and found that children and adolescents recruited VLPFC more during switching whereas adults recruited it more for rule representation (Crone et al., 2006). No

studies have used reward reversal learning paradigms in individuals with ASD, which is surprising given the vast amount of evidence for cognitive inflexibility in this patient group (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff, 1995, Ozonoff et al., 2000, McEvoy et al., 1993, Hughes et al., 1994, Bennetto et al., 1996, Coldren and Halloran, 2003, Verte et al., 2005, Yerys et al., 2007, Yerys et al., 2009, Yerys et al., 2012, Robinson et al., 2009, Van Eylen et al., 2011).

Although both switching and reward reversal learning tasks tap into cognitive flexibility, the reward aspect of reward reversal learning elicits activation in areas of reward processing such as OFC and vmPFC (Rolls, 2000, O'Doherty, 2004).

Despite the fact that cognitive flexibility is consistently impaired in ADHD (Kempton et al., 1999, Cepeda et al., 2000, Itami and Uno, 2002, Inoue et al., 2008, Oades and Christiansen, 2008, Marzocchi et al., 2008, Walshaw et al., 2010, Willcutt et al., 2005, Chamberlain et al., 2011), only a small number of studies have investigated the underlying neural substrates of cognitive flexibility in children with ADHD (Smith et al., 2006, Finger et al., 2008, Rubia et al., 2010b, Rubia et al., 2010a). Several whole brain fMRI studies used an fMRI adapted version of the Meiran Switch Task, which measures relatively simple visual spatial switching between horizontal and vertical spatial dimensions with only small loads on WM. These studies reported decreased activation in medication naïve ADHD children and adolescents in bilateral IFC, insula, superior temporal lobe, inferior parietal lobe and striatum compared to healthy control children (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a). One study that used a reward reversal learning task in 14 children with ADHD after a 48 hour medication washout showed increased activation in the ADHD group in precuneus, right superior frontal and superior temporal cortices relative to healthy controls (Finger et al., 2008).

These conflicting results may be due to the fact that reward reversal learning tasks activate areas of reward processing such as OFC and vmPFC which are not typically activated during switching tasks. Furthermore, the ADHD group in Finger et al.'s study (2008) was previously medicated, of mixed sex and had a significantly higher IQ than the control group. The other fMRI studies of cognitive flexibility in children with ADHD used medication naïve, male only, IQ matched samples; these

strengths increase the reliability of their findings (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a), especially as it has been shown that there are neurofunctional differences between males and females with ADHD (Valera et al., 2010).

In summary, children with ADHD show consistent underactivation in fronto-striatal and temporo-parietal brain regions during tasks of cognitive switching (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a). However, more research is needed using reward reversal learning tasks to test whether the deficits during cognitive switching are also observed during reward reversal learning.

3.4.2 – fMRI of Cognitive Flexibility in ASD

Despite the restrictive and repetitive behaviours observed in ASD, and the evidence for impaired switching and reversal learning (Geurts et al., 2004, Ozonoff et al., 2004, Verte et al., 2005, Sanders et al., 2008), only two whole brain studies have researched the neural substrates of cognitive flexibility in adults with ASD and they produced conflicting results (Schmitz et al., 2006, Shafritz et al., 2008). The switch task used by Shafritz et al involved shapes being shown one by one on the screen. The participants had to press one button every time they saw a target shape, and another button every time they saw a non-target shape. The target shape would switch between a triangle and a circle every after two runs and these switch trials were used to analyse brain activation during switching. Using this task, they found decreased activation in DLPFC, ACC, intraparietal sulcus, basal ganglia and insula in the left hemisphere when comparing 18 adults with HFA to typically developing adults. However, Schmitz et al (2006) found increased activation in right IFC and left mesial parietal cortex when comparing adults with HFA to controls during a visuo-spatial switch task. Only Shafritz et al (2008) observed a performance difference, finding that the HFA group were significantly less accurate in target-shift trials compared to their typically developing peers.

Both studies have their strengths and weaknesses as Shafritz et al's study had an ASD sample size of 18 with no comorbidities who had all been diagnosed using the

ADI and ADOS. However, the study was conducted on a mixed sex patient sample and one participant was taking psychotropic medication. Schmitz et al used a HFA, all male sample who were, right handed, medication naïve and had no co-morbidities. However, the patient sample consisted of only 10 HFA adults, only seven of which had been diagnosed using the ADI.

Thus, one can tentatively conclude that during tasks of cognitive flexibility adults with ASD exhibit decreased activation in left fronto-striatal regions (Shafritz et al., 2008) with some evidence for increased activation in right IFC (Schmitz et al., 2006). Surprisingly, no studies have used fMRI to investigate switching in children with ASD and no previous study has used a reward reversal learning paradigm in fMRI to elucidate the neural correlates of cognitive inflexibility in adults and children with ASD. This exposes a gap in the ASD fMRI literature and highlights the need for research to be conducted in this area.

3.4.3 – Summary of fMRI of Cognitive Flexibility in ADHD and ASD

Due to the small number of studies that have been conducted in order to elucidate the brain abnormalities present in ADHD and ASD during tasks of cognitive flexibility and reversal learning, and the incongruity of the results obtained, it is difficult to create a robust hypothesis.

Nonetheless, children with ADHD exhibited bilateral fronto-striatal and temporo-parietal deficits compared to controls during tasks of cognitive flexibility (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a), and while there is also evidence of a fronto-striatal deficit in adults with ASD, the decreased activation in these areas is more left lateralised (Shafritz et al., 2008). Another study found increased activation in right IFC in adults with HFA (Schmitz et al., 2006), which was not observed in youths with ADHD (Smith et al., 2006, Finger et al., 2008, Rubia et al., 2010b, Rubia et al., 2010a). Parietal dysfunction has been reported in both adults with ASD and children with ADHD; however, while it has been consistently shown that this dysfunction is a decrease in activation for children with ADHD (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a), there is evidence for both increased

and decreased activation in this area in adults with ASD (Schmitz et al., 2006, Shafritz et al., 2008). Children with ADHD also show deficits in temporal lobe activation during tasks of cognitive flexibility compared to their typically developing peers (Smith et al., 2006, Finger et al., 2008, Rubia et al., 2010b, Rubia et al., 2010a) and this deficit has not yet been reported in adult ASD studies.

3.5 – Other Cognitive Domains

3.5.1 – ADHD

In addition to deficits in WM, inhibition and cognitive flexibility, individuals with ADHD have also shown to be consistently impaired in timing processes, including motor timing, time estimation, time discrimination and temporal discounting (Rubia et al., 2009a, Noreika et al., 2013). Deficits in attention functions, most prominently in selective and sustained attention, have also been observed (Losier et al., 1996, Willcutt et al., 2005, Pasini et al., 2007, Rubia et al., 2007a, Sonuga-Barke, 2003, Sonuga-Barke and Halperin, 2010) as have impairments in reward processing and sensitivity (Sagvolden et al., 2005, Luman et al., 2010).

A small number of whole brain (Smith et al., 2008, Rubia et al., 2009a) and ROI (Vloet et al., 2010) fMRI studies have focused on the neural correlates of timing deficits in children with ADHD. Those that focused on time discrimination have reported decreased activation in ADHD children relative to controls in typical timing regions of right DLPFC, IFC, ACC, caudate and cerebellum (Smith et al., 2008, Rubia et al., 2009a, Vloet et al., 2010). Only one study has investigated the neurofunctional abnormalities present in ADHD children during temporal discounting and they observed reduced activation in vmPFC, striato-thalamic, parietal and cerebellar regions (Rubia et al., 2009a). A recent meta-analysis of timing processes in ADHD including 11 studies in 150 ADHD patients relative to 145 controls showed that individuals with ADHD exhibit consistently decreased activation in a predominantly left hemispheric timing network of left VLPFC, left parietal lobe and cerebellum compared to controls (Hart et al., 2012a).

fMRI research has also been conducted in children with ADHD during tasks of sustained attention in order to elucidate the neurofunctional underpinnings of their impairment in this domain (Willcutt et al., 2005). These whole brain studies reported decreased activation in ventrolateral, ventromedial and dorsolateral prefrontal cortices, as well as in parietal lobe, striatum and thalamus, which are all involved in attention (Rubia et al., 2009b, Rubia et al., 2009d, Christakou et al., 2013). These results were corroborated by a recent meta-analysis which included 13 studies that investigated attention functions in individuals with ADHD and found consistently reduced activation in 171 patients with ADHD compared to 178 controls in right DLPFC, basal ganglia, thalamus and right inferior and superior parietal lobes (Hart et al., 2013).

With regards to reward, surprisingly little fMRI research has been conducted in children with ADHD. Whole brain studies that have investigated rewarded sustained attention have reported reduced activation in PCC, precuneus and cerebellum, as well as increased OFC and temporal lobe activation in children with ADHD compared to controls (Rubia et al., 2009b, Rubia et al., 2009a). Decreased activation has also been observed in the ventral striatum of children with ADHD compared to controls during reward anticipation, and this neurofunctional abnormality was correlated with higher symptom scores as assessed by parents (Scheres et al., 2007). An ROI study also reported that during successful reward outcome, children with ADHD showed increased striatal activation compared to controls (Paloyelis et al., 2010).

3.5.2 – ASD

As stated in Chapter 1, children with ASD have difficulties in ToM. fMRI research focusing on the neurofunctional abnormalities present in children with ASD during tasks involving irony comprehension through vocal tone and facial expression, found decreased activation in typical areas of ToM such as mPFC (Gallagher and Frith, 2003, Gallagher et al., 2000, Vollm et al., 2006b), and increased activation in right inferior frontal lobe and bilateral temporal lobe compared to healthy controls when using whole brain and ROI analyses (Wang et al., 2006, Wang et al., 2007). Whole brain studies investigating ToM in adult ASD have reported decreased mPFC,

ACC, inferior OFC and amygdala activation in adults with ASD compared to age matched controls, as well as increased activation in superior temporal lobe (Baron-Cohen et al., 1999, Mason et al., 2008, Kana et al., 2009, Schroeder et al., 2010). These studies provide evidence for the presence of abnormal activation in the neural ToM network (Gallagher and Frith, 2003, Gallagher et al., 2000, Vollm et al., 2006b) in both children and adults with ASD compared to controls.

Whole brain (Manjaly et al., 2007) and ROI (Lee et al., 2007) studies investigating the neural correlates of ‘weak’ central coherence in adolescents with ASD during an embedded figures task found decreased activation in areas which have been shown to be involved in central coherence (Ferstl and Von Cramon, 2001, Ferstl and von Cramon, 2002), such as dorsal premotor regions, right superior parietal lobe, and left occipital lobe. A whole brain fMRI study of the embedded figures task in adults with ASD found decreased activation in bilateral parietal lobe and right DLPFC in addition to increased activation in right occipital lobe and inferior temporal lobe (Ring et al., 1999).

Due to the impairments in social interaction in ASD, many studies have used passive face observation, face detection and face recognition tasks to elucidate the basis of this impairment. The fMRI studies that have investigated face observation, detection and recognition have consistently found individuals with ASD to have decreased activation in lateral fusiform gyrus, a key area of face processing (Kanwisher et al., 1997, Kanwisher and Yovel, 2006, Gauthier et al., 2000, Grill-Spector et al., 2004), when compared to typically developing controls (DiCicco-Bloom et al., 2006, Schroeder et al., 2010, Minshew and Keller, 2010). These intriguing results of decreased activation in the ‘fusiform face area’ are in line with the poor facial and emotion recognition abilities in individuals with ASD (Harms et al., 2010). However, it has been suggested that this decreased activation may be due to the fact that ASD individuals are less likely to look at the eyes of the face (Harms et al., 2010), as it has been shown that activation in the lateral fusiform gyrus increases with the amount of time spent looking at the eyes (Dalton et al., 2005, Piggot et al., 2009).

Recently, the fMRI literature in ASD has focused quite intently on the mirror neuron system (MNS). The MNS is a selection of neurons that fire both when you perform a goal directed action and when you observe a goal directed action being performed by someone else (Williams et al., 2006d, Williams et al., 2001, Perkins et al., 2010, Kana et al., 2010). It was first described in non-human primates (Gallese et al., 1996, Rizzolatti et al., 1996) and has been linked to empathy (Rizzolatti and Craighero, 2004, Kaplan and Iacoboni, 2006, Gazzola et al., 2006). The mediating regions in humans are premotor regions, IFC, superior temporal sulcus and inferior parietal lobe (Rizzolatti and Craighero, 2004, Iacoboni et al., 2005, Chong et al., 2008, Kilner et al., 2009). Due to the role of imitation in social development and interaction, in addition to the imitation difficulties observed in those with ASD, research has been conducted in order to test whether individuals with ASD exhibit abnormal activity in the MNS. These studies provide some evidence for decreased activation of the MNS, particularly IFC (pars opercularis), in children and adults with ASD compared to healthy controls during tasks of imitation and imitation observation (Williams et al., 2001, Williams et al., 2006a, Dapretto et al., 2006, Perkins et al., 2010, Kana et al., 2010). However, further studies are needed to support these findings.

3.5.3 – ADHD and ASD

Despite the genetic, behavioural and cognitive overlap between ADHD and ASD (Rommelse et al., 2011) only one study has directly compared brain activation between children with ADHD, children with ASD and healthy control children (Christakou et al., 2013). During increasing loads of sustained attention, controls increased activation in DLPFC, while progressively decreasing activation in precuneus, the latter of which was thought to be representative of deactivation of the DMN. However, both patient groups exhibited decreased activation compared to controls in striato-thalamic regions, left DLPFC, pre and postcentral gyri and superior parietal lobe, as well as increased activation in the precuneus, which was thought to be indicative of impaired deactivation of the DMN. The decreased DLPFC activation was significantly greater in the ADHD group compared to the ASD group. Furthermore, the ASD group exhibited increased activation in the cerebellum

compared to both ADHD and controls boys, which was anti-correlated with DLPFC and presumably compensating for frontal deficits (Christakou et al., 2013). This seminal study has shed light on the shared and disorder-specific neurofunctional abnormalities in ADHD and ASD and highlights the need for more studies that compare these two overlapping disorders.

3.6 – Functional Connectivity

3.6.1 – Functional Connectivity in ADHD

Functional connectivity is described as the temporal correlation of the time course of brain activation in physically remote areas of the brain (Poldrack et al., 2011) and there has been increasing interest in this area in children and adolescents with ADHD.

Studies that have investigated the functional connectivity of the brain in children with ADHD during rest have observed abnormal connectivity of the DMN compared to controls (Cao et al., 2009, Castellanos et al., 2009, Fair et al., 2010, Konrad and Eickhoff, 2010, Liston et al., 2011, Tomasi and Volkow, 2011, Sun et al., 2012).

It was therefore hypothesised that in children with ADHD, decreased attenuation of this network during task performance may account for some of the neurofunctional abnormalities that are observed in task-positive regions (Konrad and Eickhoff, 2010, Castellanos et al., 2009). This hypothesis was investigated and it has in fact been shown that ineffective deactivation of the DMN is associated with more attentional lapses and worse performance in attention tasks in ADHD (Sonuga-Barke and Castellanos, 2007, Broyd et al., 2009, Konrad and Eickhoff, 2010, Christakou et al., 2013).

Only a few studies have investigated functional connectivity in children with ADHD during task performance and they have reported decreased connectivity in fronto-striato-parieto-cerebellar networks during tasks of rewarded sustained

attention, interference inhibition and timing, and motor response inhibition, relative to controls (Rubia et al., 2009b, Vloet et al., 2010, Mulder et al., 2011).

In conclusion, abnormal functional connectivity in the DMN has been observed in children with ADHD during rest, and increased activation of this network during task performance has been linked to abnormalities in task positive brain activation (Cao et al., 2009, Fair et al., 2010, Liston et al., 2011, Tomasi and Volkow, 2011, Sun et al., 2012, Konrad and Eickhoff, 2010, Castellanos et al., 2009). During tasks of timing and attention, decreased functional connectivity has been observed in fronto-striato-parieto-cerebellar networks (Rubia et al., 2009b, Vloet et al., 2010, Mulder et al., 2011). This suggests that not only are children with ADHD impaired in particular brain regions but also in the functional inter-regional interconnectivity of these regions.

3.6.2 – Functional Connectivity in ASD

There have been many studies focusing on functional connectivity in ASD in order to provide further evidence for the theory of long range under-connectivity and short range over-connectivity in ASD. As mentioned in the previous chapter, there has been a lot of interest in connectivity in ASD, particularly because it has been observed that long range connectivity increases with age while short range connectivity decreases, suggesting that individuals with ASD show an immature pattern of functional connectivity (Fair et al., 2009).

Due to the wealth of knowledge available on this topic various reviews have been published in order to clarify whether current research is consistent with the hypothesis of decreased long range connectivity and increased local connectivity in ASD (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2012, Just et al., 2012). These reviews have found a general consensus in the literature confirming the presence of decreased long range functional connectivity between fronto-cortical regions, particularly fronto-parietal connectivity, in individuals with ASD, relative to controls, during tasks of planning, cognitive flexibility, social cognition and emotion processing. However, there was less evidence for the presence

of increased short range connectivity within neighbouring areas in the frontal lobe, in this patient group (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2012, Just et al., 2012).

Furthermore, poor functional connectivity between frontal and parietal lobes has been linked to social impairment as measured by the ADI, while increased connectivity between the frontal eye field and dorsal ACC has been linked to higher levels of restrictive and repetitive behaviours (Vissers et al., 2011).

When focusing on the literature regarding resting state functional connectivity in children and adults with ASD, decreased connectivity of the DMN has been reported compared to typically developing controls (Broyd et al., 2009, Minshew and Keller, 2010, Vissers et al., 2011, Philip et al., 2011). Furthermore, the importance of this decreased resting state connectivity has been highlighted by a recent study in which abnormal resting state connectivity was used to correctly classify 89% of ASD adolescents in their sample when using machine learning (Anderson et al., 2011). It was noted that the most important connectivity areas for classification were the DMN, superior parietal lobe, anterior insula and fusiform gyrus (Anderson et al., 2011).

Although there is a general consensus on decreased fronto-posterior connectivity during tasks of planning, cognitive flexibility, social cognition and emotion processing and decreased DMN connectivity during rest in individuals with ASD compared to controls, there are also studies that have found increased connectivity in the DMN during these same tasks (Turner et al., 2006).

In summary, the current literature supports the hypothesis of decreased fronto-posterior connectivity in ASD, relative to controls, during tasks of planning, cognitive flexibility, social cognition and emotion processing. However, there is limited evidence for the presence of increased frontal to frontal connectivity (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2012, Just et al., 2012). The presence of under connectivity in the DMN during the resting state analysis has also been reported and the abnormalities in both functional and resting state connectivity have been linked to clinical symptoms of ASD (Minshew and

Keller, 2010, Vissers et al., 2011, Philip et al., 2012, Kana et al., 2011, Anderson et al., 2011).

3.6.3 – Summary of Functional Connectivity in ADHD and ASD

There is a large body of functional connectivity research in both ADHD and ASD and this has led to quite consistent results being obtained for each patient group (Castellanos et al., 2009, Cao et al., 2009, Rubia et al., 2009b, Fair et al., 2010, Minshew and Keller, 2010, Vloet et al., 2010, Konrad and Eickhoff, 2010, Liston et al., 2011, Anderson et al., 2011, Kana et al., 2011, Tomasi and Volkow, 2011, Vissers et al., 2011, Philip et al., 2012, Wong and Stevens, 2012).

During tasks of executive functions children with ADHD show under connectivity in fronto-striato-parieto-cerebellar networks compared to controls (Rubia et al., 2009b, Vloet et al., 2010) and children and adults with ASD show decreased connectivity in fronto-parietal regions during cognitive and social tasks (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2012, Just et al., 2012). Thus, both children with ADHD and children and adults with ASD appear to exhibit decreased functional connectivity in fronto-parietal networks compared to controls. However, there is some evidence that children with ADHD have under-connectivity in fronto-striatal and fronto-cerebellar networks. (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2012, Just et al., 2012, Rubia et al., 2009b, Vloet et al., 2010).

During the resting state, functional connectivity both in children with ADHD (Cao et al., 2009, Fair et al., 2010, Liston et al., 2011, Tomasi and Volkow, 2011, Sun et al., 2012, Konrad and Eickhoff, 2010, Castellanos et al., 2009) and children and adults with ASD (Minshew and Keller, 2010, Vissers et al., 2011, Philip et al., 2012, Kana et al., 2011, Anderson et al., 2011) have shown decreased connectivity of the DMN compared to controls.

In summary, it appears as if children with ADHD and children with ASD both have deficits of under-connectivity in fronto-parietal regions during tasks with a high

cognitive demand and under-connectivity in the DMN during the resting state. However, children with ADHD have also shown decreased connectivity in fronto-striatal and fronto-cerebellar networks, a deficit which has not been observed in ASD thus far (Cao et al., 2009, Fair et al., 2010, Liston et al., 2011, Tomasi and Volkow, 2011, Sun et al., 2012, Konrad and Eickhoff, 2010, Castellanos et al., 2009, Rubia et al., 2009b, Vloet et al., 2010, Wong and Stevens, 2012, Minshew and Keller, 2010, Vissers et al., 2011, Philip et al., 2011, Kana et al., 2011, Anderson et al., 2011, Just et al., 2012).

3.7 – Overall Conclusions

This chapter has reviewed the abnormalities present in children with ADHD and children and adults with ASD during tasks of WM, inhibition, cognitive flexibility and in inter-regional functional connectivity. Due to study limitations (discussed in each section), as well as the lack of research in specific areas, particularly with regards to childhood fMRI studies in ASD, it is difficult to produce a hypothesis on the potential similarities and differences of brain dysfunction present in ADHD and ASD.

However, taking these confounds into account, it has been reported that during tasks of WM, both children with ADHD and children and adults with ASD show decreased activation in IFC and parietal lobe relative to controls, although the laterality of this deficit differs between the two patient groups, with evidence suggesting that ASD individuals have more left lateralised brain dysfunctions. This evidence for decreased activation in key areas of WM in both disorders suggests that there may be similar neurofunctional deficits in ADHD and ASD underlying their cognitive impairments in this domain. However, a direct comparison between the two disorders is needed in order to ascertain whether there is a shared fronto-parietal dysfunction. It would also be of particular interest to see whether any laterality effects are observed in a direct comparison of a classic verbal WM task such as the N-Back, as previous research would suggest that children with ASD may show more left lateralised deficits (Koshino et al., 2005, Koshino et al., 2008). The N-Back has only been utilised once in an fMRI study of children with ADHD (Kobel et al., 2009) and

never in children with ASD. Therefore, the role of increasing WM load has rarely been investigated in these patient groups, and has never been directly compared. Consequently, it would be highly pertinent to assess whether deficits in DLPFC, a key area for the manipulation and storage information during WM, were present in children with ADHD and children with ASD with increasing WM load. However, it has previously been reported that increased sustained attention load did not lead to progressively increased activation in DLPFC in children with ADHD and children with ASD, relative to controls. Therefore, in this PhD an N-Back WM task was employed in the MRI scanner to investigate the potential shared and disorder-specific neurofunctional effects of increasing WM load in children with ADHD and children with ASD.

During successful inhibition of a prepotent motor response decreased activation was observed in children with ADHD compared to controls in right lateralised inhibition networks of IFC, SMA/ACC, caudate and thalamus (Tamm et al., 2004, Booth et al., 2005, Durston et al., 2006, Epstein et al., 2007, Smith et al., 2006, Rubia et al., 1999, Rubia et al., 2005, Rubia et al., 2010, Rubia et al., 2011), which are also the key areas of dysfunction found in a meta-analysis of 15 studies of motor inhibition (Hart et al., 2013). As there are no studies that have used fMRI to investigate motor response inhibition in children with ASD, only adult studies can be commented upon. Adults with ASD also exhibited decreased right frontal activation compared to controls in ACC and inferior/middle frontal cortices during motor response inhibition (Kana et al., 2007). However, it has also been shown that adults with ASD have increased activation in left IFC and left OFC during successful inhibition of a prepotent motor response (Schmitz et al., 2006). Due to the deficits in inhibition networks in children with ADHD (Hart et al., 2013), and the role of these inhibition networks in repetitive behaviours (Langen et al., 2011), it would be highly appropriate to use fMRI to directly compare the neurofunctional abnormalities present in motor response inhibition in children with ADHD and children with ASD. For this reason, in this PhD a tracking Stop Signal task was used in the MRI scanner to elucidate the potential shared and disorder-specific neural abnormalities of motor response in children with ADHD and children with ASD.

During tasks of interference inhibition, children with ADHD have shown decreased activation in inferior, and medial frontal,-striatal and temporo-parietal regions compared to healthy controls (Konrad et al., 2006, Schulz et al., 2005, Vaidya et al., 2005, Vloet et al., 2010, Rubia et al., 2009, Rubia et al., 2011a, Rubia et al., 2011b), confirmed to be consistent across studies in a meta-analysis of 6 studies of interference inhibition (Hart et al., 2013). Children with ASD have also shown decreased activation in frontal and parietal regions compared to age matched controls during interference inhibition, but this deficit appears to be more left lateralised (Solomon et al., 2009).

Relatively few studies have tested for cognitive flexibility. Compared to controls, children with ADHD and adults with ASD both exhibit IFC, DLPFC, striatal and parietal deficits; however, these deficits have been shown to be more left lateralised in adults with ASD (Shafritz et al., 2008) and more right hemispheric in ADHD (Smith et al., 2006, Rubia et al., 2009, Rubia et al., 2010). Children with ADHD have been shown to have decreased activation in temporal lobe, which has not been observed in ASD thus far (Smith et al., 2006, Rubia et al., 2010). The lack of fMRI research in children with ASD in this field is surprising, given consistent evidence for cognitive flexibility problems at the behavioural and cognitive level (McEvoy et al., 1993, Hughes et al., 1994, Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff et al., 1995, Ozonoff et al., 2000, Bennetto et al., 1996, Coldren et al., 2003, Verte et al., 2005, Yerys et al., 2007, Yerys et al., 2009, Yerys et al., 2012, Robinson et al., 2009, Velazquez et al., 2009, van Eylen et al., 2011). The interesting similarities and differences between the neurofunctional abnormalities present in children with ADHD and adults with ASD suggest that a direct comparison is warranted between the two disorders in groups of similar age. In this PhD, a reward reversal learning task was used in fMRI to uncover the potential shared and disorder-specific neural dysfunction of reward-associated cognitive flexibility in children with ADHD and children with ASD.

When assessing functional connectivity it was observed that both children with ADHD and children and adolescents with ASD have under-connectivity in fronto-parietal regions with ADHD children exhibiting this dysfunction during tasks of rewarded sustained attention and motor response inhibition (Rubia et al., 2009, Vloet

et al., 2010) and ASD individuals exhibiting this dysfunction during tasks of cognitive flexibility, planning, social cognition and emotion processing (Minshew and Keller, 2010, Vissers et al., 2011, Kana et al., 2011, Philip et al., 2011, Just et al., 2012). In addition, both disorders show under-connectivity in the DMN during the resting state (Cao et al., 2009, Fair et al., 2010, Liston et al., 2011, Tomasi and Volkow, 2011, Sun et al., 2012, Konrad and Eickhoff, 2010, Castellanos et al., 2009, Rubia et al., 2009, Vloet et al., 2010, Wong and Stevens, 2012, Minshew and Keller, 2010, Vissers et al., 2011, Philip et al., 2011, Kana et al., 2011, Anderson et al., 2011, Just et al., 2012). However, children with ADHD also exhibit decreased connectivity in fronto-striatal and fronto-cerebellar regions which has not been observed in ASD thus far.

Although poor fronto-parietal connectivity has been observed in both disorders it is elicited more by tasks of attention and inhibition in ADHD and tasks of social and emotional understanding in ASD. However, this may be due to the research bias present in both conditions, which has focused more on executive functions in ADHD and on socio-emotional functions in ASD. It would be interesting to directly compare the two disorders to investigate whether fronto-parietal connectivity deficits were present in both patient groups in tasks that are relevant both to ADHD and ASD. Direct comparison of children with ADHD and children with ASD would also clarify whether both groups show poor connectivity of the DMN during rest. This is of particular interest because DMN connectivity increases with age, so poor connectivity is suggestive of an immature DMN (Fair et al., 2008, Power et al., 2010). In this PhD I will therefore also focus on testing for task-related DMN abnormalities in both disorders.

In conclusion, during tasks of executive functions such as WM, cognitive flexibility and inhibitory functions, children with ADHD (Rubia et al., 1999, Rubia et al., 2008, Rubia et al., 2009, Rubia et al., 2010, Rubia et al., 2011, Tamm et al., 2004, Booth et al., 2005, Vaidya et al., 2005, Smith et al., 2006, Vance et al., 2007, Kobel et al., 2009) and children and adults with ASD seem to both have decreased activation in IFC and parietal lobes, but these deficits appear to be located more predominantly in the right hemisphere for children with ADHD (Rubia et al., 1999, Rubia et al., 2005, Rubia et al., 2011a, Rubia et al., 2011b, Silk et al., 2005, Booth et al., 2005, Vance et al., 2007) and more predominantly in the left hemisphere for children and adults with

ASD (Silk et al., 2005, Koshino et al., 2005, Koshino et al., 2008, Kana et al., 2007, Shafritz et al., 2008). However, children with ADHD also exhibit decreased activation in the striatum and temporal lobe during tasks of motor response inhibition and WM, which has not been observed thus far in ASD (Rubia et al., 1999, Rubia et al., 2005, Rubia et al., 2010, Durston et al., 2003, Silk et al., 2005, Booth et al., 2005, Smith et al., 2006, Epstein et al., 2007, Fassbender et al., 2009).

The only study to compare brain activation in these two disorders directly using fMRI was from our group. We showed that during a parametric task of sustained attention, the two patient groups shared deficits compared to controls in left DLPFC, striato-thalamic, superior and parietal brain regions. Also, both groups showed less deactivation of the DMN with increased sustained attention load relative to controls. However, ADHD boys were more impaired in left DLPFC activation relative to ASD boys while ASD boys appeared to activate more cerebellum compared to ADHD and control boys, which was anticorrelated with the frontal deficits, presumably to compensate for the deficits in DLPFC (Christakou et al., 2013). In conclusion we found relatively similar fronto-striato-thalamic and DMN deficits in both disorders, with more severe DLPFC deficits in ADHD and a disorder-specific fronto-cerebellar dysregulation in ASD.

There are remarkably few fMRI studies which focus on executive functions in ASD (Luna et al., 2002, Koshino et al., 2005, Koshino et al., 2008, Schmitz et al., 2006, Kana et al., 2007, Shafritz et al., 2008) and there are hardly any fMRI studies in children and adolescents (Silk et al., 2006, Solomon et al., 2009). The few existing studies have a number of limitations, including small sample sizes, inclusion of psychiatric co-morbidities, psychotropic medication and mixed sex groups, which are caveats also observed in many of the fMRI studies of executive function in children with ADHD. Small sample sizes reduce the power of the study to find subtle neurofunctional differences (Thirion et al., 2007), while psychiatric co-morbidities such as conduct disorder in ADHD (Rubia et al., 2010) and anxiety in ASD (White et al., 2009, Juranek et al., 2006) reduce the disorder-specificity of the findings of the study. It is known that psychotropic medication such as stimulants (Konrad et al., 2007, Rubia et al., 2009b, Rubia et al., 2011b, Rubia et al., 2011c) and Selective Serotonin Reuptake Inhibitors (SSRIs) (Del-Ben et al., 2005, Murphy et al., 2009,

Murphy S.E, 2010) have both short and long acting neurofunctional effects which may affect fMRI results. It is also known that there is substantial sexual dimorphism in the brain (Cosgrove et al., 2007, Sacher et al., 2012), particularly during development (Giedd and Rapoport, 2010, Sowell et al., 1999), so single sex or matched groups should be used in order to reduce the effect of sex on the results. However, the use of single sex groups is particularly relevant in ADHD and ASD, as in addition to typical sexual dimorphism, there is evidence to suggest that the clinical manifestation, cognition and neural correlates of these disorders differ between males and females (Lord et al., 1982, Arnold, 1996, Gaub and Carlson, 1997, Baron-Cohen, 2002, Valera et al., 2010, Rivet and Matson, 2011).

As mentioned in Chapter 1, there is a high level of co-morbidity between ADHD and ASD (Goldstein et al., 2004, Gadow et al., 2006, Simonoff et al., 2008, Rommelse et al., 2012), and neuropsychological studies investigating WM, inhibition and cognitive flexibility in these patient groups have found cognitive deficits in these domains in both children with ADHD (Cepeda et al., 2000, Inoue et al., 2008, Willcutt et al., 2005) and ASD compared to controls (Williams et al., 2005, Williams et al., 2006, Steele et al., 2007, Christ et al., 2007, Christ et al., 2011, Yerys et al., 2009, Van Eylen et al., 2011).

However, despite the surprisingly small number of fMRI studies on executive function in children with ASD, the caveats that are present in fMRI studies of executive function in children with ASD and children with ADHD, and the deficits in WM, inhibition and cognitive flexibility that are present in both disorders, there is only one study from our group which addressed these issues. Christakou et al (2012) used fMRI to directly compare a group of majority medication naïve, non-comorbid, age and IQ matched children with ADHD to children with ASD during a task of parametrically modulated sustained attention, finding both disorder-specific and shared brain dysfunctions.

This highlights the need for more studies that use fMRI to directly compare the neurofunctional differences and similarities in tasks in which both disorders are impaired, such as WM, inhibition, attention and cognitive flexibility, in large single sex groups of children with ADHD and children with ASD who are free of psychiatric

comorbidities and psychotropic medication. Furthermore, the modifications to the upcoming DSM-V, which allows co-diagnosis of these two overlapping disorders (<http://www.dsm5.org>), underline the importance of studies directly comparing homogenous groups of children with ADHD and children with ASD in tasks which are relevant to both disorders. Therefore, it is important for future studies to uncover the common and disorder-specific neurofunctional underpinnings of executive functions that are impaired in both disorders, as a better understanding of the differential neural correlates of these two complex and overlapping neurodevelopmental disorders may have the potential to improve both differential diagnosis and disorder-specific treatment.

In this PhD, fMRI is used to scan 22 non-comorbid children with combined type ADHD and 22 non-comorbid children with ASD (either HFA or Asperger's syndrome) while they performed a cognitive test battery involving an N-Back task, a Stop Signal task and a reward reversal learning task to investigate the neurofunctional differences and similarities in these two disorders that often exhibit overlapping symptoms and cognitive deficits.

Chapter 4 – Serotonin and its role in ADHD and ASD

4.1 – Introduction

Serotonin, often known as 5-hydroxytryptamine (5-HT), was first discovered in the late 1930s by an Italian scientist who came across a molecule that was produced by enterochromaffin cells in the gut of the rabbit and caused smooth muscle and blood vessels to contract. He named the substance enteramine and began investigating the origins and function of this newly discovered molecule (Feldman et al., 1997, Sibley et al., 2007). In the 1940s, a group of American scientists were analysing the serum of clotted blood and were able to isolate a molecule that induced contractions in smooth muscle. They named this molecule “sero-”, due to the fact it was found in serum, “-tonin”, due to the tonic effect it had on smooth muscle (Feldman et al., 1997, Sibley et al., 2007). After the molecular structure of 5-HT and enteramine were elucidated in 1952, it was discovered that 5-HT and enteramine were in fact the same molecule, and in the present day, this molecule is normally referred to as 5-HT.

The research amassed on 5-HT indicated that 90% of the 5-HT in the body was present in the enterochromaffin cells of the gastric mucosa, 8-10% in platelets, and the rest was thought to be present in small amounts in blood vessels and smooth muscles (Feldman et al., 1997, Sibley et al., 2007, Rang et al., 2012). It took a number of years before the work from the Page laboratory was able to convince the scientific community that 5-HT was present in the brain as a neurotransmitter and it is known that only 1-2% of the 5-HT in our body is found in the brain (Feldman et al., 1997). Nonetheless, 5-HT plays a pivotal role in a large number of functions mediated by the brain, such as mood regulation, aggression, sleep, arousal, impulsivity, cognitive flexibility, memory and learning (Lucki, 1998). This chapter will cover the neurobiology of the serotonergic system and the pharmacokinetics of the SSRI Fluoxetine. The way in which Fluoxetine and other methods of 5-HT manipulation have been used to shed light on the role of 5-HT in WM, inhibition and cognitive flexibility in healthy individuals will be discussed, as will the evidence for serotonergic dysfunction in ADHD and ASD.

4.2 – The Serotonergic System

5-HT is an indolamine and its production is dependent on its amino acid precursor, tryptophan. As tryptophan is an essential amino acid, the body cannot create it and depends on our dietary intake of this molecule to create 5-HT (Feldman et al., 1997, Sibley et al., 2007, Rang et al., 2012). The biosynthetic pathway which leads to the production of 5-HT involves two important enzymes known as tryptophan hydroxylase and L-aromatic amino acid decarboxylase (Feldman et al., 1997, Sibley et al., 2007, Rang et al., 2012). Tryptophan hydroxylase is the rate-limiting step of the pathway and the amount of 5-HT produced is highly dependent on the rate at which this enzyme catalyses the reaction of tryptophan to 5-hydroxy-tryptophan. The catabolism of 5-HT is catalysed mainly by the A isomer of the mitochondrial bound monoamine oxidase (MAO) enzyme, which is also involved in the catabolism of other key monoamines such as dopamine and noradrenaline. The products of the reaction between MAO and 5-HT are further broken down by aldehyde dehydrogenase to give the final waste product of 5-HT, 5-hydroxyindole acetic acid (5-HIAA), which is excreted into the cerebral spinal fluid (Feldman et al., 1997, Sibley et al., 2007, Rang et al., 2012) (Figure 1).

5-HT is the most widely dispersed neurotransmitter in the brain and its extensive neural projections are found in almost all regions (Sibley et al., 2007, Lesch and Waider, 2012). 5-HT production in the brain occurs mainly in the medulla oblongata and midbrain in nine clusters of 5-HT producing cells called nuclei. These nuclei are often referred to as B1-B9 and are split into the caudal and rostral system, with B1 being the most caudal nuclei. The caudal system consists of B1-B4 and projects mainly to the spinal cord and medulla. The rostral system consists of B5-B9 and projects mainly to the brain. The cerebellum is innervated by a mixture of caudal and rostral projections as it receives neurons from B2, B3 and B5 (Tork, 1990, Feldman et al., 1997, Sibley et al., 2007). Due to the scope of this PhD the remainder of this section will focus on the rostral system.

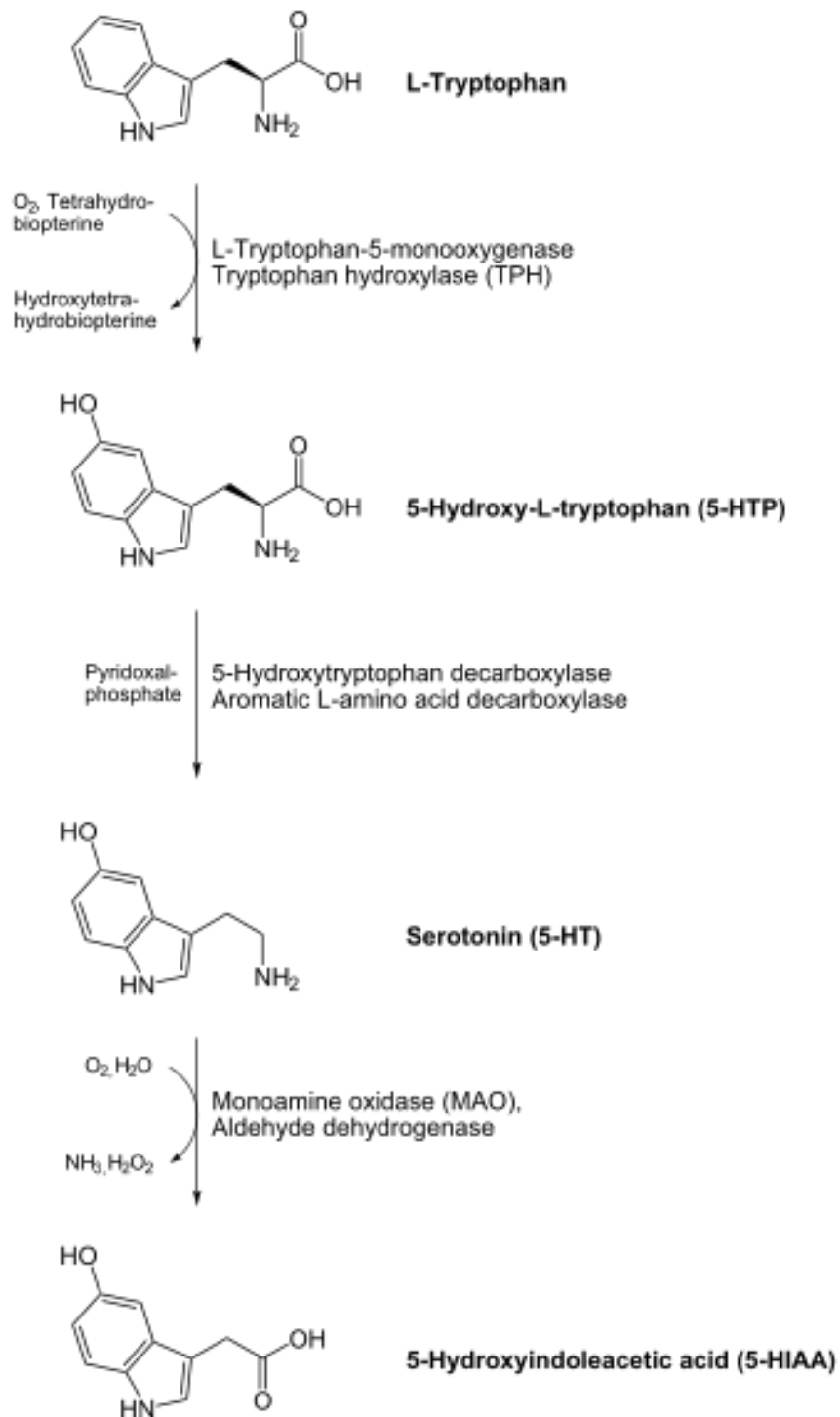


Figure 1 – Biosynthetic pathway for serotonin production (Rang et al., 2012)

The rostral system can be further divided into the dorsal raphe nucleus (DRN), which consists of B6 and B7, and the median raphe nucleus (MRN), which consists of B5, B8 and B9. The DRN contains approximately 165, 000 5-HT neurons, making it the largest collection of serotonergic neurons in the brain (Tork et al., 1990, Feldman et al., 1997). Neurons from the DRN project to the cerebral cortex, thalamus, caudate, putamen and nucleus accumbens. They also project to the substantia nigra and ventral tegmental area, highlighting the neuromodulatory role that 5-HT plays in dopamine release (Tork et al., 1990, Feldman et al., 1997, Sibley et al., 2007, Di Matteo et al., 2008). The MRN also innervates the cerebral cortex, basal ganglia and thalamus, and it sends particularly large projections to the limbic system (Feldman et al., 1997, Sibley et al., 2007). There has been evidence to show that the OFC in particular is densely innervated by the serotonergic system and that 5-HT plays an important role in its function (Roberts et al., 2011).

In addition to their slightly differing projections in the brain, the structure of the neurons emanating from the DRN and MRN also differ somewhat. Due to the large number of cells in the DRN, neurons from this area are the most common in the brain. These neurons have long, thin fibres which branch often and contain small varicosities along its length. Neurons from the MRN have much thicker fibres which branch less and have large, round varicosities (Figure 2).

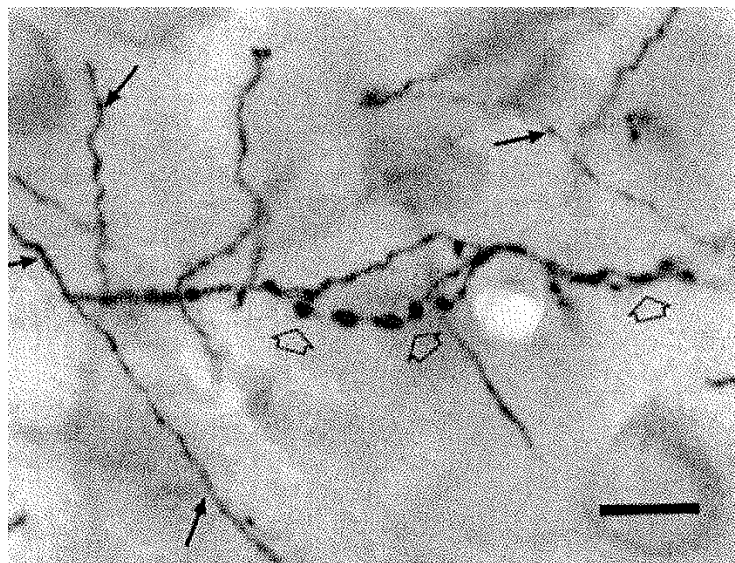


Figure 2 – Neurons of the dorsal raphe nucleus (small, thin arrows) and neurons of the median raphe nucleus (short, thick arrows) (Tork et al., 1990)

The varicosities on 5-HT neurons rarely make conventional synaptic connections and 60-80% of 5-HT undergoes non-synaptic release in what is known as volume transmission (Feldman et al., 1997, Sibley et al., 2007). Once 5-HT is released from serotonergic neurons, it can interact with a number of 5-HT receptors. There are currently 7 different classes and 14 different subtypes of receptor in the 5-HT system, all of which are part of the G-protein coupled receptor family, apart from the 5-HT₃ receptor, which is a ligand gated ion channel. As most of our knowledge regarding the receptors of the serotonergic system is founded on research into the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} receptors, this section will review the role and function of these receptors only (Sibley et al., 2007, Rang et al., 2012).

The 5-HT₁ class of receptors is the largest and consists of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}. The 5-HT_{1A} receptors act as negative feedback autoreceptors on the somatodendrites of the DRN and MRN and regulate chronic 5-HT release by hyperpolarising the neuron to reduce neuronal firing (Sibley et al., 2007, Di Matteo et al., 2008). They are present postsynaptically in the limbic system, particularly in the hippocampus, to further attenuate 5-HT release. Postsynaptic 5-HT_{1A} receptors are also present on dopaminergic neurons in the ventral tegmental area and selective 5-HT_{1A} agonists lead to an increase in dopamine in the hippocampus and prefrontal cortex (Di Matteo et al., 2008).

5-HT_{1B} receptors, much like 5-HT_{1A} receptors, are located both presynaptically and postsynaptically and can act as autoreceptors on 5-HT neurons and heteroreceptors on non-serotonergic neurons, respectively. There are a high number of 5-HT_{1B} receptors in the basal ganglia and ventral tegmental area and specific 5-HT_{1B} activation decreases 5-HT in the hippocampus and frontal cortex, but increases dopamine in the striatum (Sibley et al., 2007, Di Matteo et al., 2008).

The 5-HT₂ class of receptors consist of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. 5-HT_{2A} and 5-HT_{2C} receptors are mainly postsynaptic excitatory receptors and have quite an extensive distribution as they are found in most cortical regions in addition to the ventral tegmental area and choroid plexus. 5-HT_{2B} has a slightly more restricted expression in the central nervous system and is found in high concentration in the

cerebellum (Sibley et al., 2007, Di Matteo et al., 2008). It has been shown that activation of 5-HT_{2A} receptors can increase dopamine release in the mPFC. However, it is well known that 5-HT_{2C} is the 5-HT receptor which plays the largest neuromodulatory role in dopamine-serotonin interactions in the brain, as activation of this receptor reduces both tonic and phasic dopamine release in the mesocorticolimbic system (Sibley et al., 2007, Di Matteo et al., 2008).

It is evident that the 5-HT system extends into almost all regions of the brain, distributes 5-HT via the wide reaching method of volume transmission, and that its receptors play a large role not only in the regulation of 5-HT but of dopamine also (Tork et al., 1990, Feldman et al., 1997, Sibley et al., 2007). Therefore, it is not surprising that recent research has produced compelling evidence for the essential role of 5-HT in neurodevelopment (Daubert and Condrón, 2010, Lesch and Waider, 2012). Cell culture research and animal studies have shown that 5-HT is required for the migration and transcription of important cell adhesion molecules, as well as the insertion of AMPA receptors, all of which are key for synaptic plasticity (Daubert and Condrón, 2010, Lesch and Waider, 2012). Due to the dense serotonergic innervation of the limbic system it has been observed that this brain region and its involvement in emotional intelligence are particularly sensitive to changes in prenatal 5-HT levels (Daubert and Condrón, 2010, Bonnin and Levitt, 2011, Lesch and Waider, 2012). This leads one to question the role of 5-HT in neurodevelopmental disorders such as ASD and ADHD, where there is a wealth of evidence for structural and functional brain abnormalities, as reviewed previously.

4.3 – Selective Serotonin Reuptake Inhibitors

Due to the role of the serotonergic system in mood regulation, the receptors and enzymes involved in this neurochemical pathway have long been a target of pharmaceutical manipulation in the quest for an effective medication for major depressive disorder (Wong et al., 1995). After the relative success of tricyclic antidepressants, which non-selectively increase 5-HT in the brain, pharmaceutical companies focused on designing a medication which specifically and selectively increased the amount of 5-HT present in the synaptic cleft of serotonergic neurons in

the brain (Wong et al., 1995, Goodnick and Goldstein, 1998). In 1972, using the structure of tricyclic antidepressants as their foundation, a lab at Lilly pharmaceuticals created a drug that was able to selectively inhibit the 5-HT reuptake transporter, leading to an increase in 5-HT in the brain. This drug was named Fluoxetine and was the first SSRI to be created (Wong et al., 1995) (Figure 3).

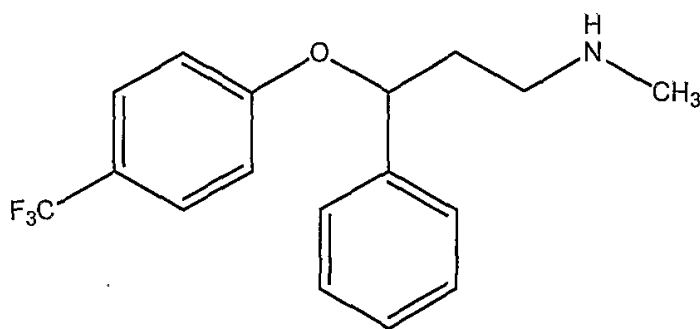


Figure 3 - Chemical structure of Fluoxetine (Wong et al., 1995)

The serotonin reuptake transporter (SERT) is a 12 transmembrane protein which is present in the presynaptic membrane of serotonergic neurons. Its role is to transport 5-HT back into the neuron from the synaptic cleft so that it can either be broken down by MAO or repackaged into a vesicle for future release (Feldman et al., 1997, Murphy et al., 2004). The SERT relies on the binding of a sodium ion and a chloride ion in addition to the binding of protonated 5-HT in order to undergo the correct conformational change to transport these molecules back into the neuron. Once 5-HT has been effectively transported, a potassium ion binds to the SERT and is transported across the membrane into the synaptic cleft. This is essential, as it causes the SERT to express its binding site on its extracellular surface once more so it is able to bind with another 5-HT molecule, or an inhibitor such as Fluoxetine (Sghendo and Mifsud, 2012).

Following the creation of Fluoxetine, five other SSRIs were designed and these were named Paroxetine, Fluvoxamine, Sertraline, Citalopram and Escitalopram (Hiemke and Härtter, 2000). Although the main method in which these drugs exert their mood regulating effect is via inhibition of the SERT, they all have very different chemical structures and therefore have quite different pharmacokinetic properties.

Fluoxetine is an equal mixture of two chemical stereoisomers named S-Fluoxetine and R-Fluoxetine. Both S and R Fluoxetine molecules contain the exact same chemical composition observed in Figure 3, but the way in which their chemical groups are arranged in 3D space differ. Stereoisomers often differ in their pharmacological potency and selectivity, and it is known that S-Fluoxetine is slightly more potent and selective for the SERT than R-Fluoxetine (Wong et al., 1995, Goodnick et al., 1998, Hiemke and Harrter, 2000). Although Fluoxetine is easily absorbed, it takes between 5-8 hours for it to reach its peak in plasma and it has a half-life of between 1-3 days (Wong et al., 1995, DeVane, 1994, Catterson and Preskorn, 1996). This relatively long half-life has been attributed to the high level of tissue accumulation and plasma protein binding that Fluoxetine undergoes, as well as the fact that it inhibits the 2D6 isomer of the cytochrome p450 liver enzyme system responsible for its metabolism (Catterson and Preskorn, 1996, Sánchez and Hyttel, 1999).

N-demethylation, the removal of a CH₃ methyl group from nitrogen, is part of the metabolism that Fluoxetine undergoes and this leads to the production of a metabolite called Norfluoxetine. Surprisingly, Norfluoxetine is a more potent and selective blocker of the 5-HT reuptake transporter than Fluoxetine, and S-Norfluoxetine is significantly more efficacious than R-Norfluoxetine (Wong et al., 1995, Sanchez et al., 1999, Hiemke and Harrter, 2000). Norfluoxetine also has a longer half-life than Fluoxetine, as it takes between 5-16 days for this metabolite to reach half its peak levels (Wong et al., 1995, Sanchez et al., 1999, Hiemke and Harrter, 2000).

Fluoxetine is specific for the SERT and although it has some affinity for the noradrenaline reuptake transporter, the amount of Fluoxetine needed to inhibit the noradrenaline reuptake transporters by 50%, known as the inhibition constant or K_i , is significantly higher than the K_i for the 5-HT reuptake transporter. This means that the amount of Fluoxetine needed to significantly inhibit the SERT is too small to have a significant effect on the noradrenaline reuptake transporters both in *in vitro* and *in vivo* experiments (Hyttel, 1994, Wong et al., 1995, Stanford, 1996).

It has been reported that Fluoxetine has an affinity for, and is an antagonist of, the 5-HT_{2C} and 5-HT_{2A} receptor (Stahl, 2009). The role that this antagonism plays in the clinical action of Fluoxetine has yet to be elucidated, but it has been postulated that it could have a role in the increase in noradrenaline and dopamine that has been observed in some animal studies despite no significant binding of Fluoxetine to the reuptake transporters of these monoamines (Stahl, 2009).

This mechanism of Fluoxetine action has been quite popular as it provides a potential explanation for the 4-6 week delay in symptom improvement that is reported in individuals with depression who are on Fluoxetine (Wong et al., 1995, Stahl, 2009). However, recent reviews and meta-analyses have shown that symptom improvement can be observed after two weeks of SSRI treatment (Taylor et al., 2006, Papakostas et al., 2006). Furthermore, changes in response to emotional faces in healthy adolescents and young adult volunteers have been observed six hours after one acute dose of Fluoxetine (Capitao et al., 2012). This rapid effect after an acute dose of an SSRI can be linked to changes in brain activation. Decreased activation in the amygdala has been observed in fMRI studies focusing on the effect of an acute clinical dose of Citalopram on emotion processing after three hours in healthy individuals (Murphy et al., 2009). This provides further evidence for the swift action of SSRIs such as Fluoxetine, on both behaviour and brain function.

Although Fluoxetine was initially created as an antidepressant, it has also been used to treat Obsessive Compulsive Disorder, anxiety disorders and eating disorders (Masand and Gupta, 1999). This has led researchers to question the role of 5-HT in cognitive processes such as inhibition, cognitive flexibility and WM. Furthermore, the relative safety and selectivity of SSRIs compared to their predecessors, in addition to the fact that Fluoxetine is the only SSRI approved for use in children and adolescents, has made investigation into the role of 5-HT in adults and children much easier.

4.4 – Serotonergic Manipulation in Healthy Humans

4.4.1 – Working Memory

WM requires the temporary storage and manipulation of information and it has been observed that tasks of WM typically recruit the DLPFC and parietal lobe (Baddeley et al., 1997, D'Esposito et al., 1998, 2000). Studies that have focused on the effect that an increase in 5-HT has on WM have produced mixed findings. Neuropsychological studies using Escitalopram in healthy adults have found no effect on spatial WM (Wingen et al., 2007), while studies using tryptophan loading and fenfluramine challenge have found that it leads to poorer WM ability (Luciana et al., 2001, Luciana et al., 1998). Acute tryptophan loading (ATL) and depletion (ATD) are popular methods of increasing and decreasing 5-HT respectively. They involve priming the body with a ratio of amino acids that will lead to an increase or decrease in tryptophan and therefore an increase or decrease in 5-HT, as dietary tryptophan is precursor of 5-HT synthesis (Mendelsohn et al., 2009, Silber and Schmitt, 2009). Fenfluramine is a molecule which increases 5-HT release by disrupting 5-HT containing vesicles in the neuron and reversing the effect of SERT. As 5-HT produces an increase in prolactin release from the pituitary gland, prolactin measurements are taken as a reflection of serotonergic function (Feldman et al., 1997).

An fMRI study using Escitalopram to increase 5-HT in a group of 10 healthy adults while they performed an N-Back task found no differences in behaviour or whole brain activation. However, ROI analysis showed that Escitalopram led to a WM load dependent increase in activation in left IFC (Rose et al., 2006).

Studies focused on elucidating the effect that a decrease in 5-HT has on WM have used ATD and they have found no effect of a decrease in 5-HT in WM ability in healthy adults (Mendelsohn et al., 2009, Harrison et al., 2004)(Harrison et al 2004, Mendelsohn et al 2009). However, an fMRI study using ATD has found that decreased 5-HT leads to decreased activation in right superior frontal cortex, and attenuation of PCC deactivation, during the 2-Back condition of the N-Back task. No behavioural differences were reported and this highlights the increased sensitivity of

fMRI to detect subtle changes between groups or conditions (Allen et al., 2006). A PET study investigating the binding potential of a 5-HT_{2A} receptor antagonist in healthy males performing a WM task found increased binding potential in OFC which the authors suggest is indicative of the increased 5-HT uptake in this area during WM (Hautzel et al., 2011).

A small number of genetic imaging studies have been conducted to assess the effect of serotonergic gene polymorphisms on WM, and the serotonergic genes that have received the most focus are the SCL6A4 gene, which codes for SERT; the 5-HT1B gene, the TPH1 and TPH2 genes, which code for the two isomers of tryptophan hydroxylase; and the MAO genes (Murphy et al., 2004, Hahn and Blakely, 2007).

There are a number of polymorphisms in the SCL6A4 gene, but the most intensely researched of these are the long (l) and short (s) alleles of the long polymorphic repeat (5-HTTLPR) region in this gene. The l allele leads to increased production of SERT and it has been proposed that this leads to lower levels of synaptic 5-HT, whereas the s allele leads to decreased SERT production and therefore increased 5-HT levels (Murphy et al., 2004, Hahn and Blakely, 2007). There is also a variable number tandem repeat polymorphism in the SCL6A4 gene known as STin2 and it has been reported that the 12 allele polymorphism of STin2 leads to increased transcription of SERT, which is proposed to lead to decreased levels of 5-HT (Murphy et al., 2004, Hahn and Blakely, 2007).

In healthy women performing an N-Back task, increased activation in left and right IFC was observed, with increasing WM load, in women with the s/s genotype of 5-HTTLPR compared to women with the l/l repeat. Women with the s/s alleles also performed poorer than women with the l/l alleles during the highest WM load (Jonassen et al., 2012). Genetic imaging studies have also investigated the effect of polymorphisms of the TPH2 gene in a group of healthy adults while performing an N-Back task and have found that individuals with the T/T polymorphism have increased activation in left DLPFC and parietal cortex with increasing WM load compared to those with the G/G or G/T polymorphisms (Reuter et al., 2008).

These studies suggest that although an increase or decrease in 5-HT may not produce a behavioural effect that is observed in a laboratory setting, it may play a role in the activity of OFC, IFC and parietal lobe, all of which are involved in WM (D'Esposito et al., 1998, D'Esposito et al., 2000, Honey et al., 2000).

4.4.2 – Inhibition and Impulsivity

It is well known that 5-HT plays a role in impulsivity (Robbins et al., 2010). For this reason, a large proportion of research into 5-HT has focused on the effect that changes in 5-HT levels play in inhibition and impulsivity. It has been observed repeatedly that SSRIs lead to decreased impulsive aggression in children and adults with impulsive aggression, and that better response to SSRI treatment is associated with the l/l genotype of 5-HTTLPR (Coccaro and Kavoussi, 1997, Armenteros and Lewis, 2002, Silva et al., 2007, Butler et al., 2010).

Studies focusing on an increase in 5-HT and its effect on motor response inhibition have found that Citalopram produces no behavioural differences in healthy adults during a Stop Signal task (Chamberlain et al., 2006). However, as with studies investigating 5-HT and WM, fMRI studies appear to produce quite different findings from neuropsychological studies; this may be due to the ability of fMRI to capture the subtle differences that are sometimes missed in neuropsychological studies.

In a group of healthy adults it has been reported that administration of Citalopram increases activation in DLPFC and right lateral OFC during successful inhibition in a Go/No-Go task (Del-Ben et al., 2005). Increased activation of right lateral OFC has also been observed in healthy males during successful inhibition in the Go/No-Go task after administration of the 5-HT_{2C} agonist mCPP, along with increased activation in caudate, superior and inferior temporal lobe and inferior parietal lobe (Anderson et al., 2002). Mirtazapine, an antidepressant which leads to increased noradrenaline and 5-HT, has also been shown to increase activation in right lateral OFC in healthy males during the successful inhibition in Go/No-Go task (Vollm et al., 2006a). Furthermore, it has been reported that daily Fluoxetine treatment for 12 weeks in adults with impulsive aggression leads to increased

metabolism in OFC and decreased aggression (New et al., 2004). This shows that there is consistent evidence that an increase in 5-HT leads to increased brain activation in key inhibition areas during successful inhibition.

A study focusing on the effects of Citalopram while healthy adults lay in the scanner found increased activation in key areas of response inhibition such as the caudate, striatum and thalamus (McKie et al., 2005). This provides evidence for the modulating effect of SSRIs in areas of motor response inhibition in the absence of a task and it has previously been reported that SSRIs sequester in the thalamus (Smith, 1999).

Neuropsychological studies investigating the effect of a decrease in 5-HT in inhibition have frequently used the Continuous Performance Identical Pairs task, where participants have to make a motor response if the number or shape shown on the screen is the same as the one before it. Studies employing this task have found that ATD leads to increased impulsivity, as evidenced by an increase in commission errors, and that this effect is increased if the participant has an s allele for 5-HTTLPR (Walderhaug et al., 2002, Walderhaug et al., 2010, Walderhaug et al., 2008). However, there is evidence that ATD does not affect motor response inhibition in healthy adults or aggressive adolescents and that it may even improve motor response inhibition (LeMarquand et al., 1998, Clark et al., 2005, Cools et al., 2005, Crean et al., 2002).

An fMRI study has shown that in a group of healthy adults performing a Go/No-Go task ATD leads to decreased activation in right IFC, a key area of inhibition, and right OFC in addition to increasing activation in left superior and right middle temporal lobe during successful no-go trials (Rubia et al., 2005a). However, there have been findings of no changes in brain activation during successful inhibition in a Go/No-Go task after ATD (Evers et al., 2006); this may be due to the fact that Evers et al used only men, since it is known that women are more sensitive to the effect of ATD (Nathan et al., 2007).

Lamar et al used fMRI to investigate the effect of ATD in a group of elderly women on a task of visuo-spatial interference inhibition. They found decreased

activation in left IFC, ACC and basal ganglia, as well as increased activation in parietal lobe and cerebellum (Lamar et al., 2009). Another study using the Stroop task to investigate the effect of ATD on interference inhibition in healthy adults found increased activation in mPFC, OFC and DLPFC (Horacek et al., 2005). These differing results may be due to the different tasks, age ranges and sexes used in the two studies and suggest that further research is needed to elucidate the effect of ATD on both motor response and interference inhibition.

Genetic imaging studies have shown that healthy adults with the l/l allele for 5-HTTLPR and MAO-A gene have decreased activation in ACC compared to carriers of the s allele and it was previously seen that this group of adults activated ACC during successful inhibition in a Go/No-Go task (Passamonti et al., 2008).

There is considerable evidence to suggest an increase in 5-HT leads to increased brain activation in key inhibition areas during successful inhibition, and this is of particular interest with regards to ADHD where fronto-striatal deficits are consistently observed during tasks of motor response inhibition (Anderson et al., 2002, Del-Ben et al., 2005, Vollm et al., 2006a, Hart et al., 2013).

4.4.3 – Cognitive Flexibility

Animal studies have consistently shown that a decrease in 5-HT impairs cognitive flexibility, particularly during tasks of reversal learning, and this has led people to investigate the effect of 5-HT manipulation on cognitive flexibility in humans (Clarke et al., 2004, Clarke et al., 2008, Clarke et al., 2005, Clarke et al., 2007, Masaki et al., 2006, Robbins, 2007).

Relatively few studies have assessed the effect that an increase in 5-HT has on cognitive flexibility. However, one study of tryptophan loading found that an increase in 5-HT had no effect in healthy volunteers with low impulsivity, but impaired switching in individuals with high impulsivity during an attentional switch task (Markus and Jonkman, 2007). A study using Escitalopram in healthy individuals also found it had no effect on reversal learning (Wingen et al., 2007). However, the task

used by Markus et al involved other processes of executive function such as selective attention, which, together with the small sample used by Wingen et al, may account for these findings.

Research into the association between cognitive flexibility and a decrease in 5-HT has shown that during a task of reversal learning, ATD in healthy volunteers reduces their ability to learn new stimulus reward contingencies and slows responding (Rogers et al., 1999, Murphy et al., 2002). However, it has also been observed that ATD produces no effect or can improve performance in healthy volunteers performing a reversal learning task (Talbot et al., 2006, Evers et al., 2005, Cools et al., 2008).

An fMRI study of ATD in healthy individuals performing a reversal learning task found that a decrease in 5-HT led to an increase in activation in dmPFC (Evers et al., 2005). The mixed findings in this field suggest that further research is needed in order to clarify the behavioural and neurofunctional effect that 5-HT manipulation has on cognitive flexibility.

4.5 – Serotonergic Abnormalities in ADHD

4.5.1 – The Dopamine Hypothesis of ADHD

Due to the rapid ameliorative affect that MPH, a form of stimulant medication which exerts its effects by blocking the dopamine reuptake transporter (Volkow et al., 1998), has in children and adults with ADHD, it has long been hypothesised that abnormalities of the dopaminergic system underlie the symptoms observed in this disorder (del Campo et al., 2011). Neuroimaging studies showing reduced dopamine binding in the striatum of medication naïve individuals with ADHD, as well as decreased activation in dopamine rich fronto-striatal areas during tasks of motor response inhibition, have supported this hypothesis (Fusar-Poli et al., 2006, Hart et al., 2013).

However, there is evidence that MPH is not effective in all cases and that its clinical efficacy wanes after 2-3 years (Jensen et al., 1997, Abikoff et al., 2004, Gualtieri and Johnson, 2008), suggesting that dopamine may not be the only neurotransmitter involved in the aetiology of ADHD. The first indication that 5-HT could be involved in the pathophysiology of ADHD came from the landmark paper by Gainetdinov et al (1999) in which dopamine knockout was used to induce a hyperdopaminergic state in mice, leading to hyperactivity. This hyperactivity was reduced by stimulants only when 5-HT was augmented, suggesting that the effect of stimulants in ADHD is mediated by 5-HT (Gainetdinov et al., 1999). As previously mentioned, dopamine and 5-HT are highly linked in the brain (Di Matteo et al., 2008) and there is consistent evidence to support the role of 5-HT in inhibition and impulsivity, both of which are diagnostic symptoms of ADHD (Coccaro and Kavoussi, 1997, Anderson et al., 2002, Armenteros and Lewis, 2002, Del-Ben et al., 2005, Vollm et al., 2006a, Silva et al., 2007, Butler et al., 2010, Robbins et al., 2010). In spite of this, there is still a dopamine bias in the ADHD literature and there has been a call for a more holistic approach with regards to research into the biochemical basis of this disorder (Oades, 2006, Oades, 2007, Oades, 2008, Oades, 2010, Rastmanesh, 2010). Research that has investigated the role of the serotonergic system in ADHD has produced intriguing results and these shall be reviewed below.

4.5.2 – Genetic

ADHD is a highly heritable disorder and this has led to a large number of genetic studies being conducted in order to try and elucidate the susceptibility genes associated with ADHD and ADHD traits (Faraone and Biederman, 2005, Gizer et al., 2009).

A recent meta-analysis has reported an association between the 1 allele of 5-HTTLPR and ADHD, suggesting that lower levels of 5-HT may play a role in ADHD (Gizer et al., 2009). This same meta-analysis also found an association between the 5-HT1B gene and ADHD and this is of particular interest because the receptor that this gene codes for is involved in inhibition of 5-HT release and increase of dopamine release (Gizer et al., 2009).

A number of recent studies have provided further support for the hypothesis that there is a genetic link between serotonergic dysfunction and ADHD. Research into the role of 5-HTTLPR in delay aversion in children with ADHD found that ADHD children with the s/l genotype were the more delay averse (Sonuga-Barke et al., 2011). Furthermore, it has been observed that children with ADHD who are homozygote for the l allele are the best responders to MPH treatment, and this highlights the importance of dopamine-serotonin interactions in ADHD (Thakur et al., 2010).

An association between the 5-HT1B gene, the 12 allele of the STin2 transcriptional regulator of SERT and risk of ADHD has been observed. It has also been reported that this 12 allele of STin2 leads to poorer response to MPH medication in children with ADHD (McGough et al., 2009, Banerjee et al., 2012).

An interest study focusing on genetic polymorphisms in the serotonergic system of mothers found that the children of women with TPH1 mutations were more likely to have ADHD symptoms, and this is in line with current research which highlights the importance of prenatal 5-HT in neural developmental (Halmoy et al., 2010, Lesch and Waider, 2012).

4.5.3 – Biochemistry

Due to the role of 5-HT in impulsivity and aggression, a number of studies have focused on the functioning of the serotonergic system in individuals with ADHD (Robbins et al., 2010).

Fenfluramine challenge has been used by a small number of studies to investigate the activity of the serotonergic system in boys with ADHD. Increased prolactin levels, and therefore increased serotonergic responsivity, was observed in aggressive ADHD boys compared to ADHD boys without aggression (Halperin et al., 1997). Another study found that serotonergic responsivity decreased over a period of 2.5 years in a group of ADHD boys (Pick et al., 1999). However, one of the main

caveats of these studies is the lack of a control group as it makes it difficult to assess the relative importance of these findings.

Research has also been conducted into 5-HIAA, which is the excretory product of 5-HT metabolism, in ADHD. Increased 5-HT metabolism (Oades et al., 1998, Oades and Müller, 1997) and a decreased dopamine:serotonin ratio (Oades and Müller, 1997), as evidenced by excretory metabolites in urine, have been reported in children with ADHD. Studies investigating cerebrospinal fluid and urinary levels of dopamine and 5-HT metabolites have also found correlations between these two neurotransmitters (Castellanos et al., 1994). This highlights the presence of serotonergic abnormalities in ADHD and its potential relationship to dopamine.

Studies using ATD in male children with ADHD after a 24 hour medication washout period have found increased laboratory provoked aggression, as well as decreased heart rate, which was used as an indicator of increased aggression, in children with ADHD after ATD (Stadler et al., 2007, Zepf et al., 2009, Zepf et al., 2008b). It has also been observed that ATD leads to an increased number of errors on the Go/No-Go task in ADHD children with high levels of aggression (Zepf et al., 2008a). A recent study has reported a decrease in lapses of attention in children with ADHD, relative to controls, two hours after receiving ATD. However, these differences were no longer observed at approximately four and five hours after ATD, which suggests that 5-HT may modulate attention functions in a different way to impulsivity (Zepf et al., 2010).

Measurements of platelet/whole blood 5-HT levels and MAO activity have been used in children with ADHD to assess the function of the 5-HT system. It has been shown that non-comorbid children with ADHD have significantly lower whole blood 5-HT levels than ADHD children who are co-morbid with CD/ODD, and that there is a trend between lower levels of whole blood 5-HT and increased ADHD severity (Cook et al., 1995, Spivak et al., 1999). When non-comorbid, medication naïve children with ADHD are compared to healthy controls, there appears to be no difference in platelet 5-HT concentrations. However, a positive correlation was observed between impulsivity and platelet 5-HT (Novkovic et al., 2009).

Research using Paroxetine binding to elucidate SERT binding on the platelets of children with ADHD found that decreased affinity was associated with poor inhibition on a Stop Signal task, suggesting that higher levels of 5-HT are associated with worse inhibition in ADHD (Oades et al., 2002).

A study has shown that medication naïve, non-comorbid children with ADHD have significantly lower MAO-B activity than their typically developing peers (Nedic et al., 2009). However as MAO-B is involved in the catabolism of 5-HT, dopamine and noradrenaline it is best to view these findings as evidence of monoamine dysfunction in ADHD as opposed to solely serotonergic dysfunction.

4.5.4 – Neuroimaging

To my knowledge, only one SPECT study has assessed SERT binding in adults with ADHD using a dopamine transporter radioligand with moderate affinity for SERT. The thalamus and midbrain were used as 5-HT specific ROIs, and although no significant differences in binding were found in the ADHD group in these regions relative to controls, the authors acknowledge that the small sample size and poor specificity of the radioligand may account for their lack of findings (Hesse et al., 2009). A SPECT study in children with foetal alcohol syndrome and ADHD found decreased 5-HT transporter binding in mPFC (Riikonen et al., 2005). However, as the main diagnosis of these children was foetal alcohol syndrome, the applicability of these findings to ADHD is limited. No fMRI study has ever investigated the role of 5-HT in children or adults with ADHD and this highlights a large gap in the ADHD literature which future research should seek to fill.

4.5.5 – Clinical Trials

There has been little research focusing on the use of SSRIs or similar medication in children and adults with ADHD. However, promising results have been produced by the studies that have.

A study of 19 children and adolescents with ADHD who took a daily dose of 20mg of Fluoxetine for six weeks after a two week stimulant medication washout found a significant improvement in Clinical Global Impression score as well as Parent and Teacher Conners' scores. Furthermore, 68% of parents wanted to continue with Fluoxetine treatment (Barrickman et al., 1991). Similar findings have been reported in a study of Fluoxetine monotherapy in 30 children and adolescents with ADHD and a comorbid mood disorder. Subjects had a 1-2 week washout of their stimulant medication and children who weighed less than 40kg were given 10mg of Fluoxetine, and children over 40kg were given 20mg daily for 6-12weeks. It was reported that 47% of participants showed a decrease in inattentive and hyperactive symptoms as well as decreased aggression. This was reflected by a significant reduction in the Conners' Parent Rating Scale (CPRS), and 83% of the children chose to continue Fluoxetine monotherapy after the trial had finished (Quintana et al., 2007).

Two studies have researched combined Fluoxetine and MPH medication in individuals with ADHD and co-morbid mood disorders. Gammon et al found that adding Fluoxetine to the normal MPH medication of 32 children for a period of 12 weeks led to a 94% improvement in ADHD symptoms (Gammon and Brown, 1993). Findling et al also found that Fluoxetine and MPH improved ADHD symptoms. However, as they observed no change in ADHD symptoms under Fluoxetine alone, they attribute the reduction in ADHD traits observed during combined therapy to MPH (Findling, 1996). This lack of improvement during Fluoxetine monotherapy may be due to the small sample size and large age range of the group, as there were only eight people in the Fluoxetine-MPH arm of this study and the study included individuals from 10-44 years old (Findling, 1996). A study investigating the effect of combined Atomoxetine and Fluoxetine medication in children with ADHD and co-morbid mood disorders observed that there was a significant improvement in both depressive and ADHD symptoms after five weeks of either Atomoxetine and placebo or Atomoxetine and Fluoxetine medication (Kratochvil et al., 2005). During the first three weeks of the study the participants were on either Fluoxetine or placebo only, but as the authors did not assess ADHD or depressive symptoms during this period of monotherapy, the effect of Fluoxetine alone cannot be compared to baseline or combination therapy (Kratochvil et al., 2005).

A small number of studies have been conducted to investigate the effect that 5-HT and noradrenaline reuptake transporter blockers (SNRIs) have on individuals with ADHD. A study focusing on the effects of the antidepressant Duloxetine in 17 children and adolescents with ADHD observed a significant improvement in scores on the CPRS (Mahmoudi-Gharaei et al., 2011). A case study on Duloxetine treatment in a 16 year old female with ADHD inattentive subtype (Niederhofer, 2010) and a 53 year old male with ADHD (Tourjman and Bilodeau, 2009) yielded similar positive results, as did a case study of milnacipran treatment in an 24 year old woman with ADHD (Kako et al., 2007). Furthermore, a recent study in which the amino acid precursors of 5-HT and dopamine were given to children and adolescents with ADHD over a 8-10 week period reported that 67% of participants had a significant improvement in ADHD symptoms (Hinz et al., 2011).

These studies highlight the ability of SSRIs and SNRIs to reduce ADHD symptoms to a clinically significant standard and it would be of great interest and relevance if future research focused on elucidating the neurofunctional underpinnings of this ameliorative effect produced by an increase in 5-HT.

4.6 – Serotonergic Abnormalities in ASD

4.6.1 – Genetic

Although a recent meta-analysis focusing on the SCL6A4 gene in ASD found no association between polymorphisms in this gene and ASD, there are a number of other genetic studies which have found associations between ASD other serotonergic genes (Huang and Santangelo, 2008).

It has been reported that polymorphisms of the 5-HT_{1B}, 5-HT_{2A} and 5-HT_{3A} gene are associated with an increased risk for autism (Orabona et al., 2009, Hranilovic et al., 2010, Anderson et al., 2009), and single nucleotide polymorphisms in the TPH2 gene have been associated with higher scores on the repetitive and stereotyped behaviours subscale of the ADI (Coon et al., 2005). Polymorphisms of the promoter

for the MAO-A gene, which leads to low activity, have been associated with increased total cortical volume in 2-3 year old boys with ASD (Davis et al., 2008).

Other genetic imaging studies focusing on the 5-HTTLPR have found that the s allele is associated with increased grey matter in the cerebral cortex of children with ASD, as well as poorer response to a 10 week course of Escitalopram and a 12 week course of fluvoxamine (Sugie et al., 2005, Wassink et al., 2007, Owley et al., 2010). Interestingly, children with ASD who possess the s allele also have more social and communication difficulties compared to ASD children with the l allele (Tordjman et al., 2001, Brune et al., 2006) and it has been shown that young adults with the s/s genotype have decreased metabolism in mPFC (Endo et al., 2010). However, it has been reported that children with the l/l genotype have more stereotyped behaviours, unusual sensory interest and increased aggression which is in line with the findings that lower levels of 5-HT are associated with aggression (Brune et al., 2006).

Thus, although the SCL6A4 gene polymorphisms may not be associated with a risk for ASD, ASD is a heterogeneous condition so SCL6A4 polymorphisms such as those of 5-HTTLPR may be associated with particular structural and functional brain abnormalities that are present in some but not all individuals with ASD, and this may have led to mixed and insignificant results.

4.6.2 – Biochemistry

In 1961 a landmark paper by Schain and Freedman found that children and adolescents with ASD had higher levels of 5-HT in their blood (Schain and Freedman, 1961). Since then, increased levels of platelet and whole blood 5-HT, known as hyperserotonemia, have been consistently reported in approximately 30% of individuals with ASD making this one of the most reproducible biological findings in Autism research (Ritvo et al., 1970, Anderson et al., 1987, Piven et al., 1991, Singh et al., 1997, Mulder et al., 2004, Hranilovic et al., 2009).

This hyperserotonemia has been linked to Autistic behaviours such as speech and language difficulties, sensory interests and self-injurious behaviour, and

highlights the potentially important role that 5-HT dysregulation plays in ASD symptoms (Kuperman et al., 1987, Cuccaro et al., 1993, Hranilovic et al., 2007, Kolevzon et al., 2009). Furthermore, higher levels of 5-HT have been observed in individuals with ASD who have a sibling with ASD compared to individuals with ASD whose sibling does not have ASD, and this suggests that there may be a genetic component to the hyperserotonemia observed in ASD (Piven et al., 1991).

A higher density of Paroxetine binding sites have been observed in the platelets of children and adolescents with ASD compared to controls suggesting an increased level of SERT (Marazziti et al., 2000, Croonenberghs et al., 2000). Lower plasma levels of tryptophan have also been reported in children with ASD compared to controls and this would be expected to lead to lower levels of 5-HT (Croonenberghs et al., 2000). A study investigating the effect of ATD in adults with ASD found that it increased ASD behaviours in 65% of the group and it was noted that patients with a higher 5-HT baseline responded worse to ATD (McDougle et al., 1996). An interesting study by Hranilovic et al separated a group of ASD adults into two groups, depending on whether hyperserotonemia was present. They then assessed the activity of SERT and MAO-B and found that individuals with ASD had significantly increased MAO-B activity compared to controls, and that this difference was more pronounced for ASD adults with hyperserotonemia (Hranilovic et al., 2009).

Interestingly, it has been suggested that hyperserotonemia in pregnant women may lead to increased risk of their children developing Autism, which is in line with recent reviews highlighting the importance of prenatal 5-HT in neural development (Hadjikhani, 2010, Daubert and Condrón, 2010, Lesch and Waider, 2012).

4.6.3 – Neuroimaging

Due to the wealth of genetic and biochemical evidence for serotonergic dysfunction in ASD, a number of neuroimaging studies have been conducted in order to uncover whether 5-HT abnormalities are present in the brains of individuals with ASD.

No fMRI study has investigated the effect of 5-HT manipulation in children with ASD. However, a SPECT study in children with ASD found decreased SERT binding in mPFC compared to their typically developing peers (Makkonen et al., 2008). A PET study in children with ASD which investigated tryptophan uptake as an indicator of 5-HT synthesis found that 55% of Autistic children showed abnormal asymmetry in their uptake of tryptophan compared to their typically developing siblings and that this was driven mainly by the decreased tryptophan uptake in the frontal lobe of children with ASD. Interestingly, it was noted that autistic children with lower tryptophan uptake in the left cortex had higher levels of speech and language difficulties (Chandana et al., 2005). A similar PET study in children with ASD found age related differences in the trajectory of 5-HT synthesis capacity, as indicated by tryptophan uptake, compared to their typically developing siblings (Chugani et al., 1999). Another study from this group found abnormal asymmetry of 5-HT in frontal cortex, thalamus and the dentate nucleus of the cerebellum synthesis for children with ASD compared to their non-autistic siblings (Chugani et al., 1997).

Adult studies have provided further evidence of serotonergic abnormalities in the brain of individuals with ASD. A recent study investigating the effects of ASD in adults with ASD during an emotional face processing task found that ASD had opposing effects in mPFC in adults with ASD compared to age matched controls (Daly et al., 2012). A case study on the neurofunctional and behavioural effect of a 12 week course of Citalopram treatment on 2 HFA males found that the participant whose symptoms improved with treatment showed increased activation in left IFC, ACC and right postcentral gyrus during an oddball task (Dichter et al., 2010).

A 16 week placebo controlled, cross-over trial of Fluoxetine in adults with ASD, in which PET scans were performed before and after Fluoxetine treatment, showed that Fluoxetine led to increased metabolic rates in right frontal lobe, ACC, OFC and striatum. This Fluoxetine induced increased metabolism was associated with behavioural improvement after Fluoxetine, showing that Fluoxetine has a positive behavioural and neurobiological effect in ASD (Buchsbaum et al., 2001).

Furthermore, adult studies have found more wide reaching 5-HT receptor deficits, with one PET study finding reduced SERT binding in all 4 lobes of the brain

as well in the limbic system, basal ganglia and thalamus in a group of 20 young adult men with ASD compared to controls. In addition to this, reduced binding in the ACC and PCC was correlated with poor social interaction skills, while reduced thalamic binding was correlated with stereotyped and repetitive behaviours (Nakamura et al., 2010).

An adult study which used SPECT to assess 5-HT_{2A} binding in young adult males with ASD found reduced binding in mPFC, ACC, PCC, bilateral frontal and superior temporal lobe and left parietal lobe. Reduced receptor binding was associated with abnormal social communication and this highlights the link between impaired serotonergic function and Autistic behaviours (Murphy et al., 2006). A recent PET study found no differences in 5-HT_{2A} binding between ASD adults and controls (Girgis et al., 2011), but these conflicting findings may be due to the use of a different neuroimaging technique and radioligand.

These studies provide strong evidence for the role of 5-HT in the abnormalities observed in the brains of individuals with ASD, and future research should focus on investigating the role of 5-HT in the neurofunctional ability of children with ASD.

4.6.4 – Clinical Trials

Research into the clinical efficacy of SSRIs in treating ASD has become quite popular due the evidence for serotonergic abnormalities in individuals with ASD and the effectiveness of Fluoxetine in treating Obsessive Compulsive Disorder and anxiety disorders which have similar symptoms to ASD (Masand and Gupta, 1999).

Studies on the effect of Fluoxetine treatment in children with ASD have found that children showed improvements in language and social communication after 2-3 years of taking 0.2mg-1.4mg/kg each day, with 50% of children being reported as having an overall good or excellent response (DeLong et al., 2002, DeLong et al., 1998). Intriguingly, it was reported that positive treatment response was correlated with unusual intellectual achievement and familial history of affective disorder (DeLong et al., 2002). Similar improvements in social communication, stereotypies

and irritability has been reported in a study including children, adolescents and young adults on a dose range of 20-80mg daily for an average of 6-18 months (Cook et al., 1992, Fatemi et al., 1998). A double-blind placebo controlled cross over trial of Fluoxetine, consisting of two 8 week phases with a 4 month washout period in between, found that a daily mean dose of 9.9mg was able to improve repetitive behaviours, as assessed by the Children's Yale-Brown Obsessive Compulsive Scale, and was globally more effective than placebo (Hollander et al., 2005). A small, six month open label trial of Fluoxetine in young autistic children, with a peak dose of 20mg, reported marked improvement on the Clinical Global Impression Scale, with decreased ritualistic tendencies and better social communication (Peral et al., 1999).

Citalopram studies have found that a 12 week course of Citalopram with a mean dose of 16.5mg daily in children and adolescents with ASD led to a significant decrease in irritability, however it was also associated with increased energy levels as defined by Clinical Global Impressions Scale (King et al., 2009). Studies using long term courses of Citalopram, with a mean course duration of approximately 7 months and a mean dose of between 16.9-19.7mg daily, found that between 59%-73% of children were significantly improved in the domains of anxiety, aggression and mood using the Clinical Global Impressions Scale (Couturier and Nicolson, 2002, Namerow et al., 2003).

There is a relatively large body of evidence to support the positive effect of Fluoxetine treatment in children with ASD and research focused on uncovering the neurobiological basis of this symptomatic improvement is very much needed.

4.7 – Summary of Serotonergic Abnormalities in ADHD and ASD

The only studies that have directly compared serotonergic function in children with ADHD and children with ASD are genetic studies, and results suggest that polymorphisms of the 5-HTTLPR may modulate ADHD and ASD severity alongside complex gene-environment interactions (Sinzig and Lehmkuhl, 2007, Nijmeijer et al., 2009, Gadow et al., 2013). Genetic studies of ADHD (Gizer et al., 2009) and ASD

(Sugie et al., 2005, Wassink et al., 2007, Owley et al., 2010) individuals alone support the potential role of 5-HTTLPR polymorphisms in each disorder, and there is evidence that 5-HT_{1B} may also be involved in both ADHD (McGough et al., 2009, Banerjee et al., 2012) and ASD (Orabona et al., 2009, Anderson et al., 2009, Hranilovic et al., 2010). However, many more studies that directly compare the role of key serotonergic genes in both ADHD and ASD are needed in order to assess whether there is any genetic overlap between the two disorders which may underlie their co-morbidity.

Children with ADHD and children with ASD appear to have very different biochemical profiles with regards to 5-HT. While there is evidence for a link between decreased 5-HT and increased aggression, impulsivity, and ADHD severity in children with ADHD (Stadler et al., 2007, Zepf et al., 2009, Zepf et al., 2010, Zepf et al., 2008a, Zepf et al., 2008b), children with ASD have higher platelet and whole blood 5-HT levels, in addition to decreased SERT binding, and this appears to be linked to symptom severity (Ritvo et al., 1970, Anderson et al., 1987, Piven et al., 1991, Singh et al., 1997, Mulder et al., 2004, Hranilovic et al., 2007). However, only 30% of individuals with ASD have this hyperserotonemia, and it has been shown that ATD leads to an increase in Autistic symptoms (McDougle et al., 1996). Therefore, more research needs to be conducted to assess the level serotonergic dysfunction present in children with ADHD and children with ASD, separately as well as comparatively.

To my knowledge, only two SPECT and no fMRI studies have been conducted on the effect of 5-HT manipulation on the brains of individuals with ADHD. Consequently, it is difficult to draw comparisons between the neurobiological differences observed in ADHD and ASD with regards to the serotonergic system. SPECT and PET studies in children with ASD have found decreased SERT binding in the mPFC as well as abnormal 5-HT synthesis and asymmetry in the brain (Chugani et al., 1999, Chugani et al., 1997, Chandana et al., 2005, Makkonen et al., 2008). No fMRI study has focused on the effects of an SSRI in children with ASD during an executive function task, but a case study in two young men with HFA have reported that Citalopram increases activation in left IFC and ACC during an oddball task (Dichter et al., 2010). This intriguing finding highlights the need for more research

focused on the neurofunctional effect of SSRIs in both children and adults with ASD, and it would be particularly interesting to directly compare the effect of an SSRI on brain activation in both ADHD and ASD.

The need for research into the effect of SSRIs in both ADHD and ASD is further supported by the finding that SSRIs, particularly Fluoxetine, have a clinically significant effect in improving both ADHD (Barrickman et al., 1991, Gammon and Brown, 1993, Quintana et al., 2007) and ASD symptoms (DeLong et al., 2002, DeLong et al., 1998, Hollander et al., 2005). Therefore, based on the genetic, biochemical and neuroimaging evidence for serotonergic abnormalities in both children with ADHD and children with ASD, in addition to the positive clinical effect SSRIs have shown in these disorders, this PhD decided to focus on the neurofunctional effect of an acute dose of Fluoxetine in children with ADHD and children with ASD during tasks of WM, motor response inhibition and reward reversal learning.

Chapter 5 – Disorder dissociated effects of Fluoxetine on areas of working memory in boys with ADHD and boys with ASD

5.1 – Introduction

ADHD is a neurodevelopmental disorder defined by age-inappropriate levels of inattention, impulsivity and hyperactivity (American et al., 1994). ASD is defined by impairments in communication, social interaction and by restricted, repetitive behaviours (American et al., 1994). However, there is increasing evidence for comorbidity between disorders (Rommelse et al., 2011), suggesting that ADHD and ASD may be part of a neurodevelopmental disorder spectrum (van der Meer et al., 2012). For instance, both disorders share deficits in executive functions (Willcutt et al., 2005, Corbett et al., 2009), including WM (O'Hearn et al., 2008, Kasper et al., 2012), and this is more pronounced at higher WM loads (Steele et al., 2007, Cui et al., 2010, Kasper et al., 2012). The importance of this clinical and behavioural overlap is highlighted by recent changes to the DSM-V - which now allows the co-diagnosis of both ADHD and ASD (<http://www.dsm5.org>).

WM is defined as the ability to temporarily store and manipulate information to guide and direct behaviour (Baddeley, 1996). A classic paradigm for measuring verbal WM is the parametric N-Back task in which subjects have to identify targets that were shown a few trials back (Baddeley, 2003). In ADHD, fMRI studies of verbal N-Back tasks show underactivation compared to controls in DLPFC, parietal lobe and right cerebellum, with more pronounced behavioural and functional deficits during higher WM loads (Kobel et al., 2009, Cubillo et al., 2013). No fMRI study has tested verbal WM in children with ASD, but adult studies have shown decreased activation in left DLPFC, left IFC and left inferior parietal lobe in the highest WM load of a verbal N-Back task (Koshino et al., 2005). Therefore, fronto-parietal dysfunction appears to be present in both disorders during verbal WM tasks with high cognitive load (Koshino et al., 2005, Kobel et al., 2009, Cubillo et al., 2013), but an important question is whether these deficits are shared or disorder-specific.

There is evidence that 5-HT is involved in verbal WM (Rose et al., 2006, Allen et al., 2006). PharmacofMRI studies using the N-Back in healthy adults have shown that Escitalopram increases activation in left IFC (Rose et al., 2006) and that ATD decreases right middle/IFC activation and attenuates DMN deactivation during high WM loads (Allen et al., 2006). Despite evidence of WM deficits in both disorders (Rommelse et al., 2011) and serotonergic mediation of the neural correlates of verbal WM in healthy individuals (Rose et al., 2006, Allen et al., 2006), few studies have investigated the clinical efficacy of SSRIs in ADHD and ASD. Fluoxetine, for example, has been shown to improve aggression, irritability, inattentiveness and hyperactivity in children with ADHD (Barrickman et al., 1991, Gammon and Brown, 1993, Quintana et al., 2007) and to improve communication, social interaction and stereotyped behaviours in children with ASD (West et al., 2009), although other SSRIs such as Citalopram have been shown to be ineffective (King et al., 2009). Nevertheless, an important question that may elucidate potential differential neurotransmitter underpinnings of cognitive abnormalities is whether 5-HT modulates verbal WM networks in ADHD and ASD and whether this modulation differs between disorders.

The aim of this fMRI study was therefore to investigate 1) disorder-specific brain dysfunctions in children with ADHD and children with ASD during a verbal N-Back task, and 2) disorder-specific neurofunctional effects of an acute dose of Fluoxetine on these (dys)functions. Based on previous findings, we hypothesised that, under placebo, both disorders would show reduced left DLPFC and parietal activation, with ADHD patients exhibiting additional right DLPFC and cerebellar abnormalities (Kobel et al., 2009, Cubillo et al., 2013, Koshino et al., 2005), and that these abnormalities would be normalised by Fluoxetine in both disorders.

5.2 – Methods

5.2.1 - Participants

Thirty - two ADHD boys were recruited in total; however, seven boys dropped out of the study due to their dislike of the MRI scanner, three were excluded due to co-morbidities, one boy did not reach the diagnostic criteria for the combined subtype of ADHD, one boy was excluded due to poor task performance and three were excluded due to high levels of motion. Forty - four ASD boys were recruited in total. Of these, seven boys dropped out of the study due to their dislike of the MRI scanner, 14 were excluded due to co-morbidities, one was excluded due to neurological abnormalities, two were excluded due to SSRI use, one was excluded due to poor task performance and two were excluded due to high levels of motion. Thirty - two controls were recruited in total however 10 were excluded due to high scores on the SDQ (Goodman and Scott, 1999) and CPRS (Conners et al., 1998) .

Fifty-six right handed boys (assessed with the Edinburgh Handedness Inventory (Oldfield, 1971)) (22 controls, 17 with ADHD and 17 with ASD) aged 10-17 years old, with an IQ > 70 (assessed with the Wechsler Abbreviated Scale of Intelligence-Revised (Wechsler, 1999) participated.

ADHD boys met DSM-IV diagnostic criteria for hyperactive-impulsive/inattentive combined type ADHD and scored above clinical threshold for ADHD symptoms on the SDQ (Goodman and Scott, 1999) and the CPRS (Conners et al., 1998); one boy was below cut-off on SDQ but had diagnostic confirmation from a child psychiatrist. Three of the ADHD boys were medication-naïve, one had ceased taking MPH for three months and 13 received chronic stimulants, but had a 48hr medication washout prior to scanning.

ASD diagnosis was made using ICD-10 (World et al., 1994) diagnostic criteria and confirmed by the ADI (Lord et al., 1994) and the ADOS (Lord et al., 2000). All ASD subjects were medication-naïve apart from one patient, who took melatonin but underwent two week medication washout. ASD exclusion criteria included a score

above 7 on the hyperactivity/inattention subscale of the SDQ. ADHD boys were excluded if they scored above 15 on the Social Communication Questionnaire (SCQ) (Rutter et al., 2003). Comorbidity with other psychiatric or neurological disorders, and drug/alcohol dependency were exclusion criteria for all patients. Patients were recruited from local clinical services and support groups. Written informed consent/assent was given for all participants and the study was approved by the local Ethical Committee.

Patients were scanned twice in a double-blind, randomised, placebo-controlled design, using a Latin square randomisation design for counter-balanced effects. Due to the half-life of Fluoxetine (1-3 days), and its metabolite Norfluoxetine (5-16 days) (Wong et al., 1995), each scan was 3-4 weeks apart. To ensure that Fluoxetine had reached its peak plasma levels, which occurs after 5-8 hours (Wong et al., 1995), patients were scanned five hours after administration. Liquid Fluoxetine was titrated to age and weight in the following manner: boys between 10-13 years and less than 30kg received 8mg, those greater than 30kg received 10mg; boys between 14-17 years and less than 30kg received 10mg, those greater than 30kg received 15mg. Placebo was equivalent amounts of peppermint water which was similar in taste to Fluoxetine.

Twenty-two healthy, age and handedness matched control boys were recruited locally by advertisement and scored below clinical thresholds on the SDQ, SCQ and CPRS.

5.2.2 - fMRI N-Back Paradigm

Subjects practiced the task once before scanning. The six minute block design WM task (Ginestet and Simmons, 2011) consists of four conditions. During “1-Back”, “2-Back” and “3-Back” conditions, subjects are presented with series of letters (A-Z) (1s duration, intertrial interval: 2 secs) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively (e.g. 2-Back:B/J/A/J) (see Figure 4). This requires both storage and continuous updating of stimuli being held in WM. In the baseline vigilance “0-Back”

condition, subjects must respond to each X that appears on the screen. The task consists of 12 randomised blocks. Before each block, written instructions of a 3 second duration are shown as to which condition is next (i.e., “0-Back”;”1-Back”; etc). In each of the WM blocks of 30 second duration only one WM condition is presented (i.e. 2-back), and contains fifteen stimuli: three targets and twelve non-targets. Each condition is presented three times. Performance data were recorded during scanning. The dependent variable is accuracy (percentage of correctly identified targets).

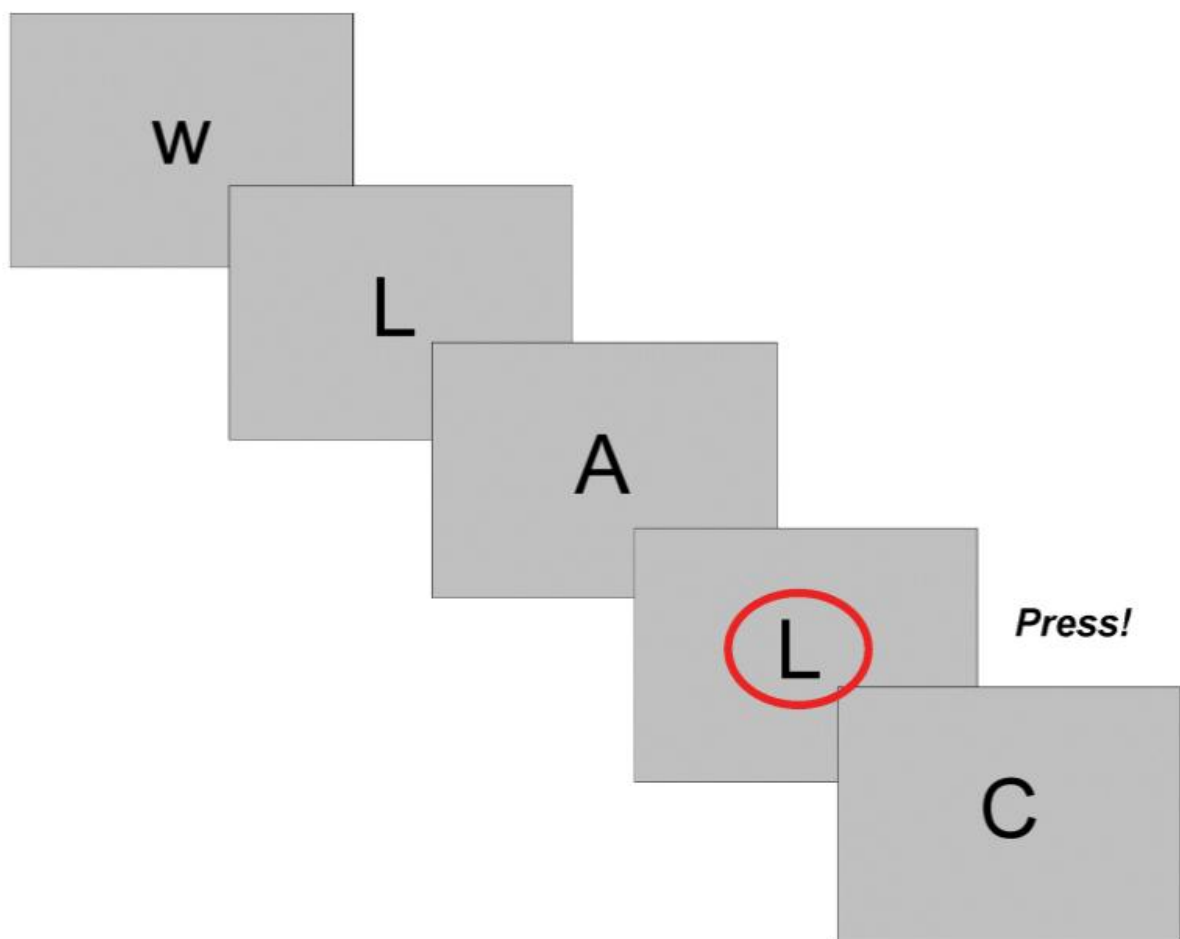


Figure 4 – The N-Back task: The six minute WM task consists of four different conditions. In the control condition “0-Back” the subject is presented to series of letters, and the subject has to press for every X that appears on the screen. In the conditions “1-back”, “2-back” and “3-back”, the subject has to press the button whenever the letter presented is the same as one, two or three before it, respectively. The image corresponds to the 2-Back condition.

5.2.3 - Data Analysis

Analysis of performance data

For the main performance measure of accuracy a repeated measures analysis of variance (ANOVA) within patients was conducted with drug condition (placebo, Fluoxetine) and WM-load (1-Back, 2-Back, 3-Back) as within-subject factors and group as between subjects factor. For case-control comparisons, two repeated measures ANOVAs (controls vs ADHD and ASD under placebo; controls vs ADHD and ASD under Fluoxetine) were conducted with WM-load as the within-subjects factor and group as the between-subjects factor.

fMRI Image acquisition

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a General Electric Signa 3T Horizon HDx system at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, UK. A semi-automated quality control procedure ensured consistent image quality (Simmons et al., 1999). A quadrature birdcage headcoil was used for radio frequency transmission and reception. In each of 39 non-contiguous planes parallel to the anterior-posterior commissure line, 186 T2*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with TE=30ms, TR=2s, flip angle=75°, in-plane voxel size=3mm, slice thickness=3.5mm, slice-skip=0.5mm. This EPI dataset provided complete brain coverage.

fMRI image analysis

Blocked fMRI data were acquired in randomised block presentation and analysed using the XBAM software package (<http://www.brainmap.co.uk>) (Brammer et al., 1997) which makes no normality assumptions (often violated in fMRI data), but instead uses median statistics to control outlier effects and permutation rather than normal theory-based inference (Thirion et al., 2007).

Individual Analysis: fMRI data were first processed to minimise motion related artifacts (Bullmore et al., 1999). A 3D volume consisting of the average

intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images. After preprocessing, time series analysis for each subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore et al., 2000, Bullmore et al., 1999). At the individual subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each N-Back task condition (1-Back; 2-Back; 3-Back) against an implicit baseline (0-Back). Briefly, we first convolved the main experimental conditions (1-Back; 2-Back; 3-Back; contrasted with 0-Back) with two Poisson model functions (peaking at 4s and 8s) after motion correction, global detrending and spin-excitation history correction. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2000) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Activated voxels, at a <1 level of type I error, were identified through the appropriate critical value of the SSQ-ratio from the null distribution. Individual SSQ-ratio maps were then transformed into standard space, first by rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

Group Analysis: A group activation map was produced for each experimental condition (1-Back; 2-Back; 3-Back; contrasted with 0-Back) by calculating the median observed SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The voxel-level threshold was first set to 0.05 to give maximum sensitivity and to avoid type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each data set, giving excellent Type II error control (Bullmore et al., 1999). Cluster mass rather than a cluster extent threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). In all group activation analyses, less than one false positive activation locus was expected for $p < 0.05$ at voxel level and $p < 0.01$ at cluster level.

Investigation for a group by WM load interaction effect on brain activation

To test for group by WM load interaction effects on brain activation, we conducted a repeated measures ANCOVA with rotational and translation movement in Euclidian 3-D space as covariate, group as between-subject variable and WM load as within-subject variable. For this purpose, we conducted randomisation-based tests for voxel or cluster-wise differences as described in detail elsewhere (Cubillo et al., 2013). A significant WM load effect was shown in 12 clusters in: right DLPFC, left DLPFC/IFC, ACC/SMA, right IFC/basal ganglia/thalamus, left basal ganglia/thalamus, thalamus/midbrain, left precentral/postcentral gyri, right precentral/postcentral gyri, right precentral gyrus, precuneus/cuneus, left PCC and right PCC. BOLD response was extracted for each region and each group. This showed that for all 3 groups, activation in bilateral ACC/SMA, DLPFC, IFC, basal ganglia, thalamus, midbrain, precuneus and cuneus increased progressively with increasing WM load, while activation in precentral/postcentral gyri and PCC was progressively more deactivated with increasing WM load (see Figure 5). However, no group by WM load interaction was observed. Consequently, we focused on the 3-Back vs 0-Back contrast in all subsequent analyses as this contrast elicited the strongest brain activation for all groups.

Working Memory Load Effect in Controls, ADHD and ASD

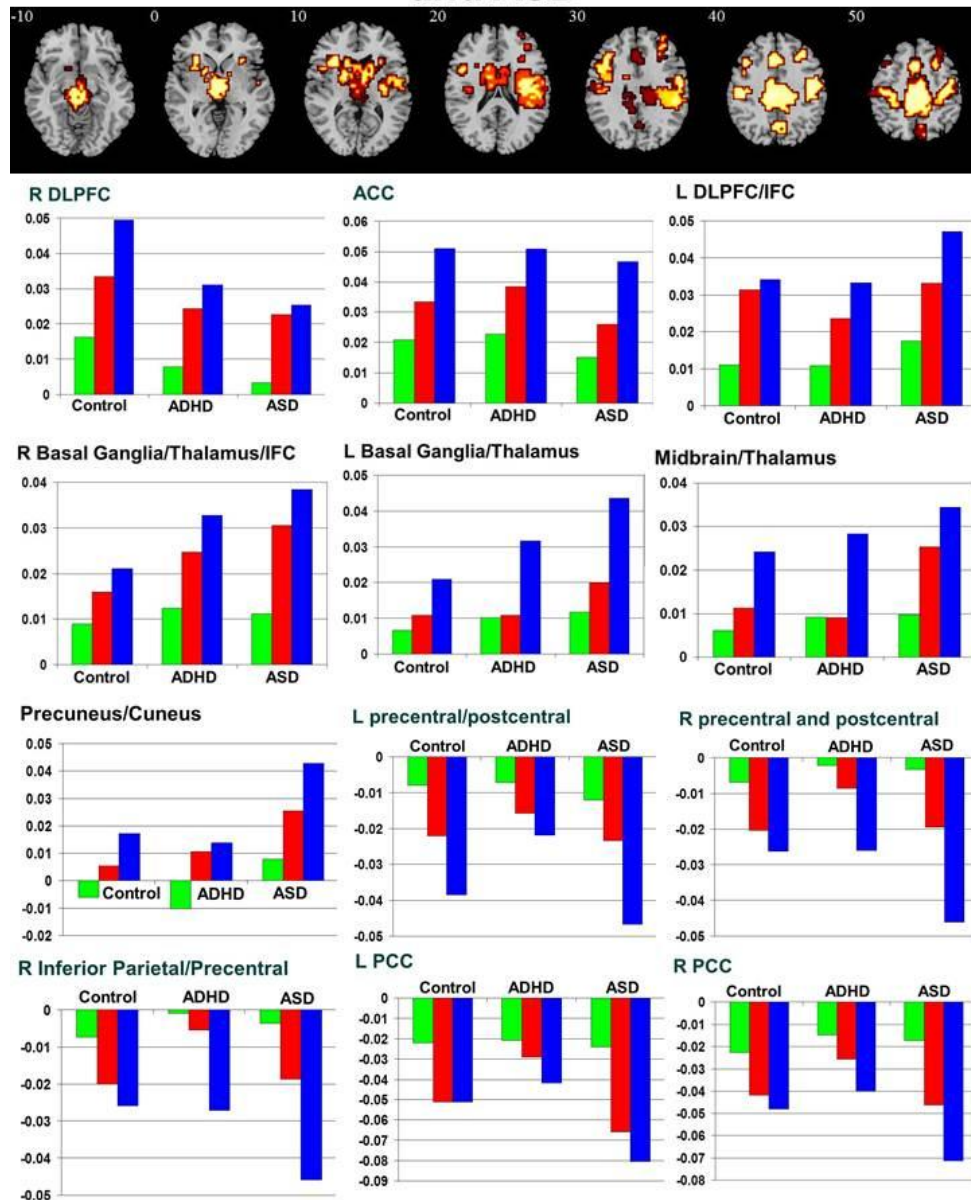


Figure 5 – Brain activation for working memory load effect in controls, boys with ADHD under placebo and boys with ASD under placebo. Axial sections showing brain activation for increasing WM load in healthy control boys, boys with ADHD under placebo and boys with ASD under placebo. Shown underneath are the statistical measures of BOLD response each of the brain regions that showed a significant WM load effect in all three groups. Green = 1-Back; Red = 2-Back, Blue = 3-Back. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image.

ANCOVA Between-Group Difference Analyses: For between-group comparisons between controls and patients under either placebo or Fluoxetine for the 3-Back condition, one-way ANCOVA analyses with group as factor and rotational and translation movement in Euclidian 3-D space as covariate, were conducted. For these between-group comparisons, less than one false activated cluster was expected at $p < 0.05$ for voxel and $p < 0.01$ for cluster comparisons. The standardised BOLD response values (SSQ ratios) for each participant were then extracted for the mean activation of each of the significant clusters of the 3-group ANCOVA analyses and post-hoc t-tests (correcting for multiple comparisons using least significant difference (LSD)) were conducted to identify the direction of the group differences.

ANCOVA Within-Patients Interaction Effects: In order to investigate group by drug interaction effects between placebo and Fluoxetine within the patient groups, a 2x2 ANCOVA (2 medication conditions, 2 groups) with rotational and translation movement in Euclidian 3-D space as covariate was conducted using randomised-based testing for voxel or cluster-wise differences. Less than one false positive 3D cluster was expected at $p < 0.05$ at voxel and $p < 0.01$ at the cluster level. Statistical measures of BOLD response for each participant were then extracted in each of the significant clusters and post-hoc t-tests (correcting for multiple comparisons with LSD) were conducted to identify the direction of the interaction effects.

Normalisation Effects: To test for the statistical significance of any apparent normalisation effects of Fluoxetine on case-control activation differences observed under placebo, we used non-parametric Friedman two-way analysis of variance by ranks on the extracted BOLD responses during each medication condition for each of the clusters shown to be significantly different in the comparison between controls and patients during placebo. We conducted this test only within patients, given that controls were only tested once, and hence constant across comparisons.

Correlations with Behaviour and IQ: To test whether group, or group by drug, interaction effects were related to clinical behaviour or IQ we correlated activation in clusters that differed between groups with the SDQ hyperactive/inattentive subscale and CPRS scores in the ADHD group. In the ASD group we correlated activation with the social and communication, and stereotyped behaviours, subscales of the

ADOS. Activation and full scale IQ was correlated in each group. For this purpose, the BOLD response was extracted for each subject and Pearson correlations were performed between these and behavioural and IQ scores.

5.3 – Results

5.3.1 - Participant Characteristics

Group differences in age and IQ

ANOVAs showed no significant group differences in age, but did for IQ ($F(df = 2, 55) = 15, p < 0.0001$) which was significantly lower in ADHD relative to control and ASD boys ($p < 0.0001$), who did not differ. ADHD children have a typically lower IQ than their healthy peers (Bridgett and Walker, 2006). Therefore, IQ was not covaried, as covarying for a measure that is intrinsic to the condition, and hence differs between groups, which were not randomly selected, would violate ANCOVA assumptions (Dennis et al., 2009). Furthermore, WM is included in the Wechsler Intelligence Scale for Children (4th version) (WISC-IV) (Wechsler, 2004) and shares a common neurological correlate in DLPFC, which would mean that covarying for IQ would also covary for the function of interest (Conway et al., 2003).

Group differences in clinical measurements

Multivariate ANOVA showed a significant group effect for all SDQ measures ($F(df = 10, 100) = 21, p < 0.0001$). Post-hoc analyses showed that controls scored significantly better on all subscales compared to patients ($p < 0.01$). ADHD boys scored significantly higher than ASD boys on the conduct and hyperactive/inattentive subscales of the SDQ ($p < 0.0001$). ASD boys scored significantly worse than ADHD boys on the peer relations subscale ($p < 0.005$) and significantly higher on the SCQ ($F(df = 2, 50) = 112, p < 0.0001$) than ADHD ($p < 0.0001$) and controls participants ($p < 0.0001$), while ADHD participants scored significantly higher than controls ($p < 0.0001$). ADHD boys scored higher on the CPRS ($F(df = 2, 52) = 136, p < 0.0001$) than ASD ($p < 0.0001$) and controls ($p < 0.0001$) and ASD participants scored higher than controls ($p < 0.0001$) (Table 1).

Table 1. Sample characteristics for control boys, boys with ADHD and boys with ASD

Variables	Controls (22) Mean (SD)	ADHD (17) Mean (SD)	ASD (17) Mean (SD)
Age (years)	14.0 (2.6)	14.7 (1.9)	15.2 (1.8)
IQ	111 (13)	93 (9)	114 (14)
SDQ Hyperactive/Inattentive Subscale	2.0 (1.8)	8.9 (1.4)	4.7 (1.9)
SDQ - Emotional Distress Subscale	0.9 (1.6)	3.2 (3.0)	4.3 (3.0)
SDQ - Conduct Subscale	0.5 (0.9)	4.6 (2.1)	2.2 (2.1)
SDQ – Peer Relations Subscale	.9 (1.2)	3.6 (2.3)	6.1 (2.4)
SDQ – Prosocial Behaviour Subscale	8.7 (2.3)	6.3 (2.3)	4.8 (2.2)
SDQ – Total scores	4.3 (4)	20.4 (4.9)	17.4 (5.9)
SCQ Total	1.8 (2.8)	8.1 (4.1)	23.4 (5.6)
CPRS Total T score	44 (4)	83 (8)	59 (9)
ADOS Communication scores	-	-	2 (1)
ADOS Social Interaction scores	-	-	7 (4)
ADOS Social and Communication scores	-	-	9 (5)
ADOS Stereotyped behaviour scores	-	-	1 (1)
ADI Communication scores	-	-	15 (4)
ADI Social Interaction scores	-	-	17 (4)
ADI Stereotyped behaviour scores	-	-	5 (3)

5.3.2 - Performance Data

Case-controls comparisons showed that across all subjects there was a significant linear WM load effect under both placebo ($F(df = 2, 52) = 49$, $p < 0.0001$) and Fluoxetine ($F(df = 2, 31) = 35$, $p < 0.0001$) showing lower accuracy in the more difficult conditions. However, no group effect was observed. Within-patient repeated measures ANOVA showed a trend for a drug effect ($F(df = 1, 32) = 3$, $p < 0.1$) due to both patient groups being more accurate under Fluoxetine than under placebo ($p < 0.08$). No other effects were significant (Table 2).

Table 2 - Performance measures for the N-Back task for controls, boys with ADHD and boys with ASD

Performance measure	Controls Mean (SD)	ADHD Placebo Mean (SD)	ADHD Fluoxetine Mean (SD)	ASD Placebo Mean (SD)	ASD Fluoxetine Mean (SD)
Accuracy 1-Back	96 (9)	95 (7)	94 (10)	99 (4)	98 (6)
Accuracy 2-Back	91 (11)	74 (24)	84 (15)	88 (17)	95 (10)
Accuracy 3-Back	70 (18)	65 (19)	68 (28)	75 (24)	78 (19)

5.3.3 - fMRI Data

Movement

Repeated measures ANOVAs using group as an independent factor and maximum x, y z rotation and translation as repeated measures showed that there were no significant group by movement interaction effects in rotation ($F(df = 4, 106) = 1$, $p = n.s.$) or translation ($F(df = 4, 106) = 2$, $p = n.s.$). Nevertheless, to eliminate any potential effects of even small, non-significant variance in motion, motion parameters were used as a covariate in the fMRI analyses.

Group Brain Activation Maps

3-Back – 0-Back

Controls – During 3-Back – 0-Back controls activated a bilateral WM network consisting of inferior/middle/superior frontal cortices, ACC/SMA, basal ganglia, thalamus, parietal lobe, precuneus, cerebellum/midbrain and left middle temporal lobe.

ADHD – While under placebo, the ADHD group activated bilateral inferior/middle frontal cortices, left precentral gyrus, ACC/SMA, bilateral basal ganglia and thalamus, right parietal lobe, precuneus, left middle/superior temporal lobe, left occipital lobe and midbrain/left cerebellum. While under Fluoxetine, they activated bilateral superior/inferior/middle frontal cortices, ACC/SMA, bilateral basal ganglia and thalamus, bilateral parietal lobe, precuneus, right inferior/middle temporal lobe, bilateral midbrain/cerebellar vermis.

ASD – While under placebo, the ASD group activated bilateral inferior/middle frontal cortices, left superior frontal cortex, left precentral gyrus, ACC/SMA, bilateral basal ganglia and thalamus, bilateral parietal lobe, precuneus, bilateral middle/superior temporal lobe, midbrain/cerebellar vermis and right cerebellum. While under Fluoxetine, the ASD group activated bilateral superior/inferior/middle frontal cortices, left precentral gyrus, ACC/SMA, bilateral basal ganglia and thalamus, bilateral insula, bilateral parietal lobe, precuneus, left

middle/superior temporal lobe, right inferior/middle temporal lobe, left middle occipital lobe, midbrain/cerebellar vermis and left cerebellum/fusiform gyrus (Figure 6.A)

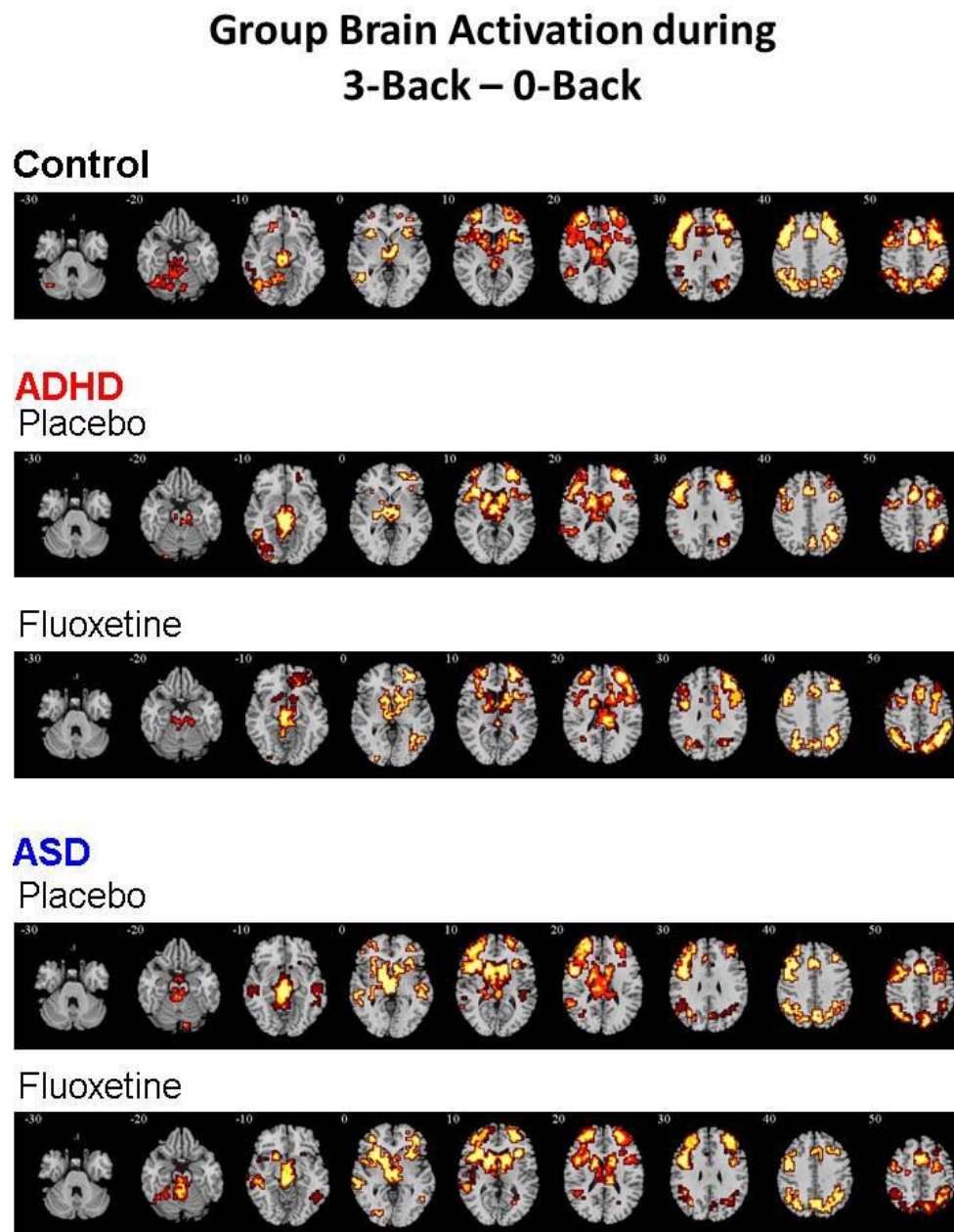


Figure 6.A – Within-Group activation for controls, and patients under either placebo or Fluoxetine, for the contrast of 3-Back – 0-Back. Axial sections showing within-group brain activation for healthy control boys, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of 3-Back – 0-Back. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image.

0-Back – 3-Back

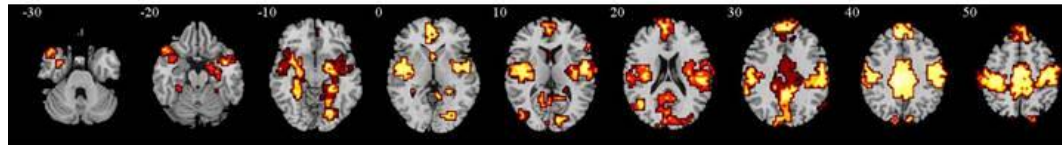
Controls – During 0-Back – 3-Back controls activated DMN areas consisting bilaterally of mPFC, precentral and postcentral gyri, putamen and caudate, insula, middle/superior temporal lobe, PCC, cuneus, fusiform gyrus and right middle occipital lobe.

ADHD – While under placebo, the ADHD group activated mPFC, left inferior/superior frontal cortex, bilateral precentral and postcentral gyri, left inferior parietal lobe, right middle/superior temporal lobe, bilateral insula/putamen, PCC, precuneus/cuneus, right lingual/fusiform gyrus and right cerebellum. While under Fluoxetine, they activated mPFC, left superior frontal cortex, bilateral IFC, bilateral precentral and postcentral gyri, bilateral inferior parietal lobe, right middle/superior temporal lobe, bilateral insula/putamen and thalamus, PCC and precuneus/cuneus.

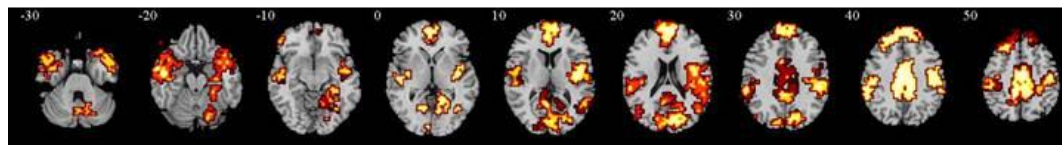
ASD – While under placebo, the ASD group activated mPFC, right superior frontal cortex, bilateral precentral and postcentral gyri, bilateral inferior parietal lobe, bilateral middle/superior temporal lobe, left putamen, right lentiform nucleus/insula, PCC, precuneus/cuneus, right fusiform gyrus and cerebellum. While under Fluoxetine, the ASD group activated mPFC, left inferior/superior frontal cortices, bilateral precentral and postcentral gyrus, , left putamen, right lentiform nucleus/insula, bilateral superior temporal lobe, left middle temporal lobe, PCC, precuneus/cuneus, bilateral occipital lobe, bilateral fusiform gyrus and cerebellum (see Figure 6.B)

Group Brain Activation during 0-Back – 3-Back

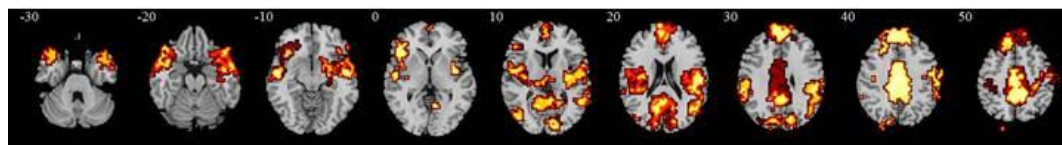
Control



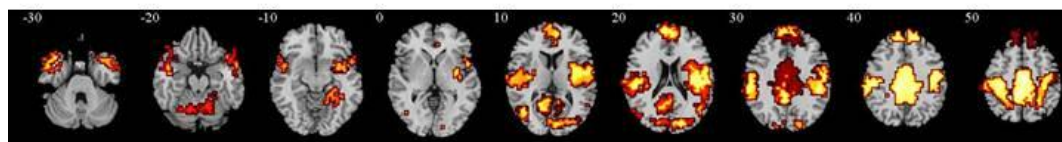
ADHD Placebo



Fluoxetine



ASD Placebo



Fluoxetine

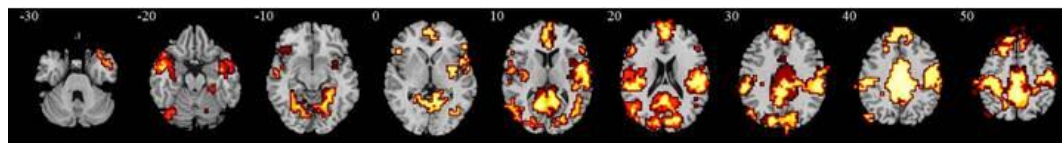


Figure 6.B –Within-Group activation for controls, and patients under either placebo or Fluoxetine, for the contrast of 0-Back – 3-Back. Axial sections showing within-group brain activation for healthy control boys, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of 0-Back – 3-Back. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image. The right side corresponds to the right side of the image.

Between-group differences between controls and patients under placebo for 3-Back

ANCOVA analysis between controls and patients under placebo for the 3-Back condition showed a significant group effect in right DLPFC and PCC (Figure 7.A, Table 3). Post-hoc analyses showed that the group effect in right DLPFC was due to significantly decreased activation in this region in the ASD ($p < 0.0001$) and ADHD ($p < 0.05$) groups relative to controls, and there was a trend-wise difference for significantly decreased activation in ASD compared to ADHD boys ($p < 0.08$). In PCC, the ASD group had significantly increased deactivation compared to both controls ($p < 0.0001$) and ADHD participants ($p < 0.005$), who also deactivated this cluster, but did not differ from each other (Figure 7.A, Table 3). No significant correlations between brain activation and behaviour or brain activation and IQ were observed.

Between-group differences between controls and patients under Fluoxetine for 3-Back

ANCOVA analysis of controls and patients on Fluoxetine showed a significant group effect in PCC, as observed under placebo, but no longer in DLPFC (Figure 7.B, Table 3). Post-hoc analyses showed that both ADHD ($p < 0.0001$) and ASD boys ($p = 0.008$) deactivated PCC more than controls.

Friedman two-way analysis of variance by ranks to test for significant normalisation showed that Fluoxetine relative to placebo significantly increased activation in right DLPFC in the ASD group only $\chi^2 (1, N=17) = 7.12$, $p = 0.008$), while in the ADHD group this was not significant, suggesting significant normalisation of this brain dysfunction in ASD only. There was a trend for Fluoxetine relative to placebo to increase deactivation of the PCC in ADHD $\chi^2 (1, N=17) = 2.88$, $p < 0.09$).

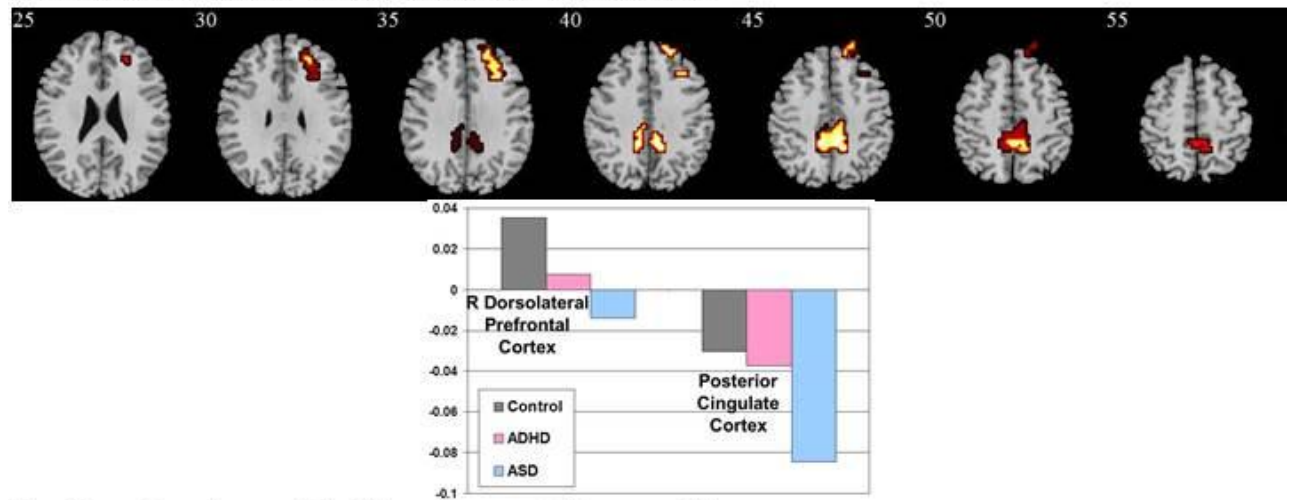
Correlations with behaviour showed that there was a positive correlation between PCC activation and scores on the hyperactive/inattentive subscale of the SDQ in the ADHD group ($r=0.578$, $p < 0.05$) and PCC activation and scores on the social/communication subscale of the ADOS in the ASD group ($r = 0.564$, $p < 0.05$). No significant correlations between brain activation and IQ were observed.

Within-Patients group by medication interaction effects

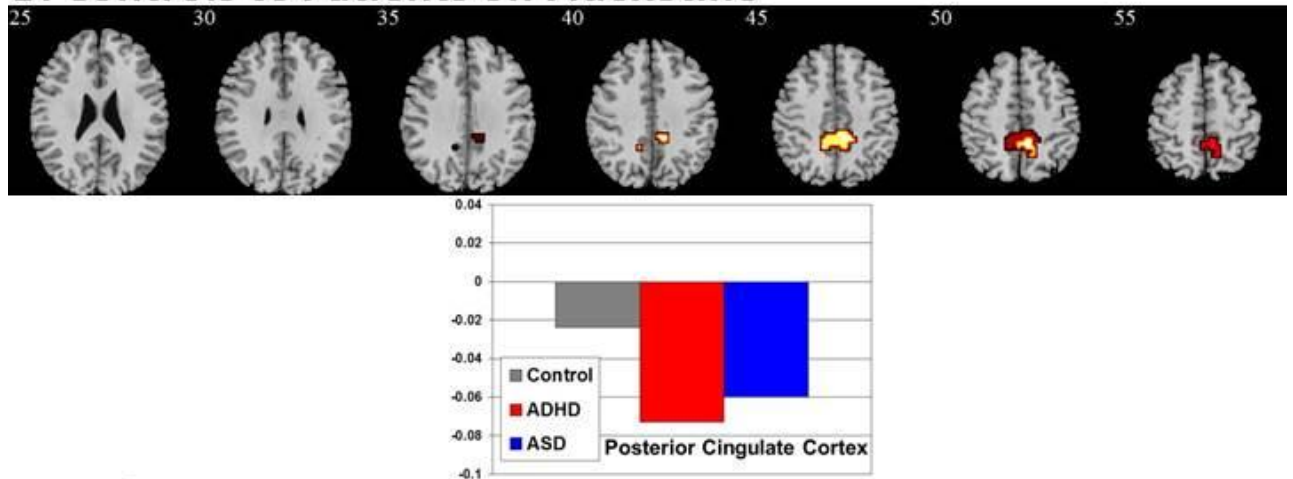
Within-patients ANCOVA analysis with group as dependent variable and drug as within-group variable showed a significant group by medication interaction effect in one cluster in PCC (74 voxels, peak Talairach coordinates (x;y;z): 11;-30;37; Brodmann area (BA): 31/24). This was due to Fluoxetine increasing deactivation of this area in the ADHD group and attenuating the deactivation in the ASD group ($p < 0.005$) (Figure 7C). No significant correlations between brain activation and behaviour or brain activation and IQ were observed.

Between-Group Comparisons

A. Controls vs Patients on Placebo



B. Controls vs Patients on Fluoxetine



Within-Patient Comparisons

C. Group by Medication Interaction Effects

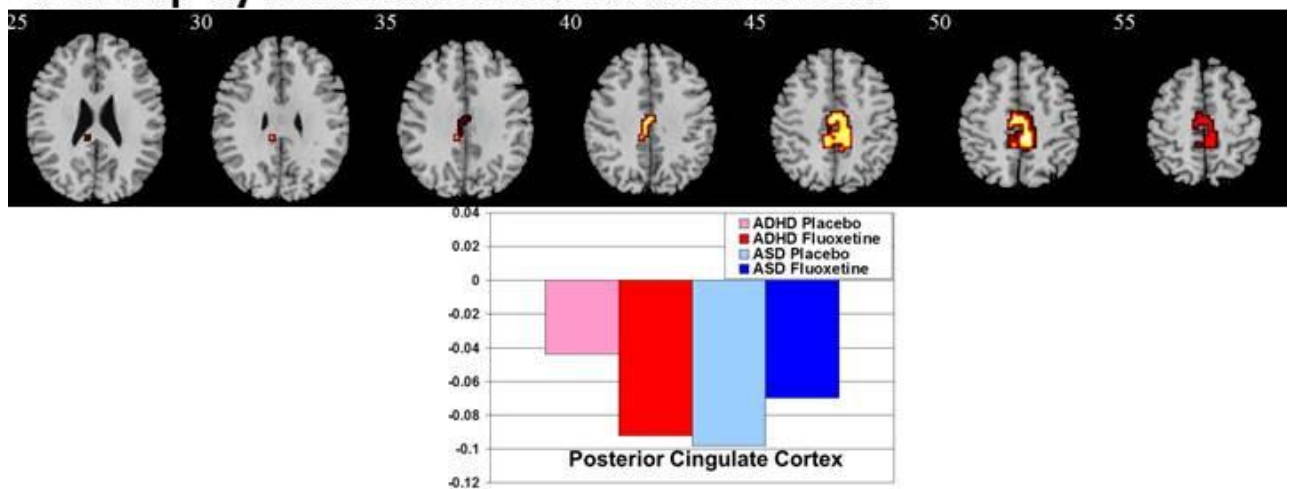


Figure 7.A. Working Memory Between-Group and Within-Patient Comparisons:

Axial sections showing the between-group ANCOVA findings between controls and patients under placebo. Shown underneath are the statistical measures of BOLD response for each of the three groups for each of the brain regions that showed a significant group effect. **B.** Axial sections for the between-group ANCOVA comparison between controls and patients under Fluoxetine. Shown underneath are the statistical measures of BOLD response for each of the three groups for each of the brain regions that showed a significant group effect. **C.** Axial sections showing within-patient group by medication interaction effects. Shown underneath are the statistical measures of BOLD response for each of the brain regions that showed a significant group by medication interaction effect between patients. Talairach z coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 3. Brain activation differences during WM between controls and patients on either placebo or Fluoxetine

Post-Hoc Group Differences	Brain regions of activation differences	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p-value
PLACEBO					
ADHD, ASD < C	R DLPFC	9/8	29;33;26	36	0.007
ASD < C, ADHD	PCC/Precuneus	31/7	-4;-33;37	70	0.0006
FLUOXETINE					
ASD, ADHD < C	PCC/Precuneus	31/7	-11;-37;37	49	0.003

5.4 – Discussion

This study shows that while performing a WM task under placebo, ADHD and ASD boys share brain underactivation relative to controls in right DLPFC, a key area for WM (Wager and Smith, 2003), which at a trend-level was more severe in ASD relative to ADHD. Furthermore, ASD boys showed disorder-specific increased deactivation of PCC compared to controls and ADHD boys. Fluoxetine at a trend-level improved performance in both disorders relative to placebo, but had a disorder-dissociated effect on task-positive and task-negative activation clusters. Fluoxetine, significantly normalised the right DLPFC deficit in ASD, while it only non-significantly normalised it in ADHD. However, Fluoxetine significantly increased the deactivation of the PCC, a DMN region, in ADHD boys and within-patient analyses confirmed that Fluoxetine significantly enhanced PCC deactivation in ADHD, but attenuated deactivation in ASD. The findings thus show both shared (DLPFC underactivation) and disorder-specific (PCC deactivation in ASD) brain dysfunctions during WM in both disorders as well as disorder-dissociated drug-effects on task-positive and task-negative activations, with Fluoxetine normalising task-positive right DLPFC underactivation in ASD, but enhancing task-negative PCC deactivation in ADHD, both leading to improved WM performance.

The shared underactivation relative to controls in right DLPFC, a key area of manipulation of information during WM (Wager and Smith, 2003), during a verbal N-Back task replicates previous findings of DLPFC underactivation in ADHD children (Cubillo et al., 2013) and adults (Valera et al., 2010) during a verbal N-Back task and also echoes consistent DLPFC underactivation in a meta-analysis of attention tasks (Hart et al., 2013). The novelty is the finding of right DLPFC underactivation in ASD during a verbal WM task and that this was trend-wise more impaired than in ADHD. The finding extends previous findings of left DLPFC underactivation in adult ASD during a verbal N-Back task (Koshino et al., 2005). The findings of shared DLPFC deficits extend prior evidence for shared reduction in left DLPFC activation during a parametric sustained attention task in ADHD and ASD (Christakou et al., 2013), suggesting that DLPFC dysfunction during attention tasks may be shared between the

two overlapping neurodevelopmental disorders and possibly play a role in the comorbidity reported between the two disorders (Rommelse et al., 2011).

The disorder-specific increased deactivation of PCC, a key region of the DMN, in the ASD group compared to controls and ADHD may have been a compensation for their DLPFC underactivation given that deactivation of the DMN is typically anti-correlated with task positive activation in DLPFC (Christakou et al., 2013) and is associated with better task performance (Northoff et al., 2010).

Under Fluoxetine right DLPFC underactivation appeared normalised in both groups, but rigorous normalisation testing showed significance only for ASD. However, Fluoxetine led to increased deactivation of PCC in ADHD, which while not different from controls under placebo, was now significantly more pronounced relative to controls under Fluoxetine. This disorder differential effect of Fluoxetine on a task-positive area in ASD (DLPFC) and a task-negative DMN area in ADHD (PCC) is interesting given that Fluoxetine improved accuracy in both disorders, at a trend-level. It suggests that Fluoxetine had a positive effect on performance and brain activation in both disorders but via different underlying mechanisms: namely, by decreasing task-unrelated thinking processes mediated by the DMN in ADHD, which has been shown to interfere with task-positive activation and lead to poor attention in the disorder (Christakou et al., 2013), and by enhancing a key task-positive area of WM in ASD.

The disorder-specific effects on DLPFC activation and the inverse effects on PCC in both disorders may be due to differences in underlying biochemical abnormalities the two disorders. Approximately 30% of individuals with ASD have hyperserotonemia (Hranilovic et al., 2007). Reduced binding to the SERT and the 5-HT_{2A} transporter in the frontal lobe and PCC have also been reported, the latter of which has been linked to poor social communication (Murphy et al., 2006, Nakamura et al., 2010). Furthermore, abnormal 5-HT synthesis has been observed in children with ASD (Chandana et al., 2005, Chugani et al., 1999, Chugani et al., 1997). This suggests that hyperserotonemia may be an adaptation to counteract poor 5-HT receptor binding and abnormal 5-HT synthesis. The increase in 5-HT with Fluoxetine may have increased ligand-receptor binding sufficiently to enhance activation in areas

where 5-HT receptor density is typically low (Nakamura et al., 2010, Murphy et al., 2006). This would be in line with, and extends prior evidence that, SSRIs increase metabolic and neurofunctional activity in prefrontal areas in adults with ASD which was associated with an improvement in ASD behaviour (Buchsbaum et al., 2001, Dichter et al., 2010).

Conversely, in ADHD there is evidence for lower platelet 5-HT levels compared to controls (Spivak et al., 1999) as well as genetic (Gizer et al., 2009) and biochemical serotonergic dysfunction (Oades, 2007). Therefore, the increase in 5-HT induced by Fluoxetine may not have been sufficient to normalise their DLPFC deficit. The increased deactivation of PCC in ADHD under Fluoxetine may be due to the effect of an increase in 5-HT on the 5-HT_{2C} receptors in this area which would lead to a decrease in dopamine (Di Matteo et al., 2008). There is consistent evidence for decreased dopamine levels in individuals with ADHD in the basal ganglia and cingulate gyrus (Volkow et al., 2005, del Campo et al., 2011) so an increase 5-HT may have decreased the already low dopamine levels in the ADHD group, leading to deactivation of this area. Interestingly, ATD in healthy adults during a verbal N-Back led to a decrease in right DLPFC activation and attenuation of PCC deactivation (Allen et al., 2006), which suggests that these brain regions are particularly sensitive to 5-HT manipulation during verbal WM and are often modulated in an inverse manner.

The strengths of this study are the carefully selected, non-comorbid patient groups who were free of psychiatric co-morbidities and, in the case of the ASD group, medication naïve. A limitation of this study is that the control group was only scanned once, while patients were scanned twice which could have accounted for the lack of performance differences. The significantly lower IQ in the ADHD group is another limitation. However, none of the brain activation effects were correlated with IQ, suggesting that IQ did not play a key role in the findings.

In summary, ADHD and ASD patients showed shared underactivation in right DLPFC, a key area for WM, with ASD patients showing more pronounced deactivation of PCC relative to both groups. Fluoxetine had a disorder-dissociated region-specific effect of significantly normalising the DLPFC deficit in ASD, but

enhancing deactivation in PCC in ADHD, which at a trend-level was concomitant with better task performance. The region-specific disorder-dissociated effects of Fluoxetine may be due to the differing biochemical abnormalities underlying the two disorders.

Chapter 6 – Inverse effects of Fluoxetine on frontal inhibitory brain activation in boys with ADHD and boys with ASD

6.1 – Introduction

ADHD is a neurodevelopmental disorder defined by age-inappropriate levels of inattention, impulsivity and hyperactivity (American et al., 1994). In contrast ASD is defined by impairments in communication, social interaction and by restricted and repetitive behaviours (American et al., 1994). However, there is increasing evidence for comorbidity between disorders (Rommelse et al., 2011) suggesting that ADHD and ASD may be part of a neurodevelopmental disorder spectrum (van der Meer et al., 2012). For instance, both disorders share executive function deficits (Willcutt et al., 2005, Corbett et al., 2009), in particular in motor response inhibition (Willcutt et al., 2005, Robinson et al., 2009) which furthermore has been associated with impulsiveness in ADHD and motor stereotypies in ASD (DSM-IV, (Langen et al., 2011). This overlap was highlighted by recent changes to the DSM-V - which now allows the co-diagnosis of both ADHD and ASD (<http://www.dsm5.org>).

In ADHD, the neurofunctional correlates of inhibition are well established with consistent evidence of underactivation compared to controls in IFC, SMA and caudate/thalamus (Rubia et al., 1999, Rubia et al., 2005b, Hart et al., 2012b). In children with ASD, however, no study has investigated the neurofunctional underpinnings of inhibition. In adults with ASD, fMRI studies report inconsistent findings of increased activation in left IFC and decreased activation in right IFC and ACC (Schmitz et al., 2006, Kana et al., 2007). Therefore, a key question to elucidate the pathophysiology of these two disorders, is whether the underlying neurobiology of shared cognitive phenotypes is shared or disorder-specific.

There is evidence that 5-HT is involved in impulsiveness and motor inhibition (Robbins et al., 2010). Pharmacological fMRI studies in healthy adults show that SSRIs and ATD enhance and decrease activation in IFC and striatal inhibition areas, respectively (Del-Ben et al., 2005, Rubia et al., 2005a). Despite evidence for

inhibitory deficits in both disorders (Rommelse et al., 2011) and serotonergic mediation of inhibitory control in healthy individuals (Del-Ben et al., 2005, Rubia et al., 2005a, Robbins et al., 2010), few studies have investigated the clinical efficacy of SSRIs in ADHD and ASD. Those that have, have used Fluoxetine and it has been shown to improve aggression, irritability, inattentiveness and hyperactivity in children with ADHD (Quintana et al., 2007) and to improve communication, social interaction and stereotyped behaviours in children with ASD (Hollander et al., 2005), although other SSRIs like Citalopram have been shown to be ineffective (King et al., 2009). Nevertheless, an important question that may elucidate potential neurotransmitter underpinnings of cognitive abnormalities, is whether 5-HT modulates the inhibitory network in both ADHD and ASD and whether this modulation differs between disorders.

The aim of this fMRI study was therefore to investigate 1) shared and disorder-specific brain dysfunctions in children with ADHD and children with ASD during a Stop Signal task and 2) shared and disorder-specific neurofunctional effects of an acute dose of Fluoxetine on these inhibitory (dys)functions in both disorders. Based on our previous findings we hypothesised that, under placebo, ADHD boys would show decreased activation in IFC and caudate compared to controls (Rubia et al., 1999, Hart et al., 2012b, Rubia et al., 2005b), whereas ASD boys would show increased left frontal activation (Schmitz et al., 2006). We further hypothesised that Fluoxetine would increase the reduced fronto-striatal activation in ADHD, but reduce the increased left frontal abnormalities in ASD.

6.2 – Methods

6.2.1 - Participants

Thirty - two ADHD boys were recruited in total; however, seven boys dropped out of the study due to their dislike of the MRI scanner, three were excluded due to co-morbidities, one boy did not reach the diagnostic criteria for the combined subtype of ADHD, one boy was excluded due to poor task performance and two were excluded due to high levels of motion. Forty - four ASD boys were recruited in total.

Of these, seven boys dropped out of the study due to their dislike of the MRI scanner, 14 were excluded due to co-morbidities, one was excluded due to neurological abnormalities, two were excluded due to SSRI use and one was excluded due to poor task performance. Thirty - four controls were recruited in total but nine were excluded due to high scores on the SDQ and CPRS.

Sixty - two right handed boys (assessed with the Edinburgh Handedness Inventory (Oldfield, 1971)) (25 controls, 18 with ADHD and 19 with ASD) aged 10-17 years old, with an IQ > 70 (assessed with the Wechsler Abbreviated Scale of Intelligence-Revised (Wechsler, 1999) participated.

ADHD boys met DSM-IV diagnostic criteria for hyperactive-impulsive/inattentive combined type ADHD and scored above clinical threshold for ADHD symptoms on the SDQ (Goodman and Scott, 1999) and CPRS (Conners et al., 1998). Four of the ADHD boys were medication-naïve, three had ceased taking MPH for a year (one), or 3 months (two) and 11 received chronic stimulants, but had a 48hr medication washout prior to scanning.

ASD diagnosis was made using ICD-10 diagnostic criteria (Organization, 1993) and confirmed by the ADI (Lord et al., 1994) ADOS (Lord et al., 2000). All ASD subjects were medication-naïve apart from one patient, who took melatonin (but underwent two week medication washout). ASD exclusion criteria included a score above 7 on the hyperactivity/inattention subscale of the SDQ or a t-score above 70 on the DSM-IV subscale of the CPRS. ADHD boys were excluded if they scored above 15 on the SCQ (Rutter et al., 2003). Comorbidity with other psychiatric or neurological disorders, and drug/alcohol dependency were exclusion criteria for all patients. Patients were recruited from local clinical services and support groups. Written informed consent/assent was given for all participants and the study was approved by the local Ethical Committee.

Patients were scanned twice in a double-blind, randomised, placebo-controlled design, using a Latin square randomisation design for counter-balanced effects. Due to the half-life of Fluoxetine (1-3 days), and its metabolite Norfluoxetine (5-16 days) (Wong et al., 1995), each scan was 3-4 weeks apart. To ensure that Fluoxetine had

reached its peak plasma levels, which occurs after 5-8 hours (Wong et al., 1995), patients were scanned five hours after administration. Liquid Fluoxetine was titrated to age and weight in the following manner. Boys between 10-13 years and less than 30kg received 8mg, those greater than 30kg received 10mg. Boys between 14-17 years and less than 30kg received 10mg, those greater than 30kg received 15mg. Placebo was equivalent amounts of peppermint water with similar taste to Fluoxetine.

Twenty-five healthy, handedness, and age-matched control boys were recruited locally by advertisement and scored below clinical thresholds on the SDQ, SCQ and CPRS.

6.2.2 - fMRI Stop Signal Paradigm

Subjects practised the task once prior to each scan. The nine minute visual tracking Stop Signal task requires withholding of an already triggered motor response to a go stimulus when it is followed unpredictably by a stop signal (Rubia et al., 1999). Subjects have to respond as quickly as possible to left or right pointing “go” arrows (500ms duration; 80% of trials) with a left or right (thumb) button press, followed by a gap of 1100 to 1500ms (mean ITI: 1.8s; jittered between 1.6 and 2 seconds to optimize statistical efficiency). In 20% of trials, pseudo-randomly interspersed, and at least three repetition times apart for adequate separation of the hemodynamic response, go signals are followed (about 250ms later) by arrows pointing upwards (stop signals), and subjects have to inhibit their motor response. A tracking algorithm changes the time interval between go and stop-signal onsets according to each subject’s inhibitory performance, which is recalculated after each stop signal based on the average percentage of inhibition over previous stop trials to provide 50% successful and 50% unsuccessful inhibition trials (see Figure 8). In the fMRI analysis, brain activation to the 50% unsuccessful stop trials is subtracted from the 50% successful stop trials, controlling for the attentional oddball effect of the infrequent stop signal appearance.

The main dependent variable of the task is the SSRT, calculated by subtracting the mean stop signal delay (SSD: the average time between go and stop signal, at

which the subject managed to inhibit to 50% of trials) from the mean reaction time (MRT) to go trials, i.e. MRT-SSD (Logan et al., 1997). MRT, intrasubject Standard Deviation of MRT (SD MRT), and omission error percentage measure the executive process of the task.

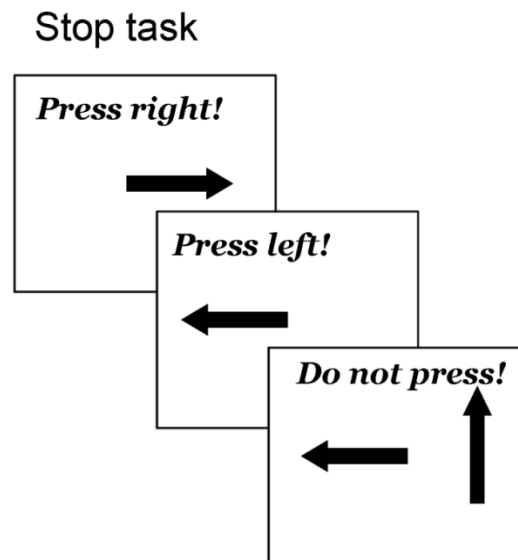


Figure 8 – The Stop Signal task. Subjects have to respond to go arrows that point either right or left with a right/left button response. In 20% of trials (the go-signals were followed (about 250ms later) by stop signals and subjects had to inhibit their motor responses. A tracking algorithm changed the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials.

6.6.3 - Data Analysis

Analysis of performance data

Multiple ANOVAs compared the main performance variables between controls and patients under placebo and Fluoxetine. Multiple repeated-measures ANOVAs within the patient groups with group as independent factor and placebo/Fluoxetine as repeated measure were conducted to test for group by medication interaction effects on performance.

fMRI Image acquisition

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a General Electric Signa 3T Horizon HDx system at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, UK. A semi-automated quality control procedure ensured consistent image quality. A quadrature birdcage headcoil was used for RF transmission and reception. In each of 28 non-contiguous planes parallel to the anterior-posterior commissure, 296 T2*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with TE=30ms, TR=1.8s, flip angle=75°, in-plane voxel-size=3mm, slice thickness=5.5mm, slice-skip=0.5mm. A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) on which to superimpose the individual activation maps, was also acquired in the inter-commissural plane with TE=30 ms, TR=3s, flip angle = 90°, 43 slices, slice thickness=3.0mm, slice skip=0.3mm, in-plane voxel-size = 1.875mm.

fMRI image analysis

The XBAM software package was used (<http://www.brainmap.co.uk>) (Brammer et al., 1997) which makes no normality assumptions (often violated in fMRI data), but instead uses median statistics to control outlier effects and permutation rather than normal theory-based inference (Thirion et al., 2007).

Individual Analysis: fMRI data were first processed to minimise motion related artifacts (Bullmore et al., 1999). A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images. After preprocessing, time series analysis for each subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore et al., 1999, Bullmore et al., 2000). At the individual subject level, a standard general linear

modelling approach was used to obtain estimates of the response size (beta) to the Stop Signal task conditions (successful and failed stop trials) against an implicit baseline (go trials) and then again for the higher level contrast of successful-go trials minus unsuccessful-go trials. Briefly, we first convolved the main experimental condition (successful and failed inhibitory trials, each separately contrasted with Go trials) and the higher level contrast (successful-go trials minus unsuccessful-go trials) with two Poisson model functions (peaking at 4s and 8s) after motion correction, global detrending and spin-excitation history correction. We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2000) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Activated voxels, at a <1 level of type I error, were identified through the appropriate critical value of the SSQ-ratio from the null distribution. Individual SSQ-ratio maps were then transformed into standard space, first by rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

Group Analysis: A group activation map was produced for the experimental condition (Successful Stop—Unsuccessful Stop) by calculating the median observed SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The voxel-level threshold was first set to 0.05 to give maximum sensitivity and to avoid type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary

combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each data set, giving excellent Type II error control (Bullmore et al., 1999). Cluster mass rather than a cluster extent threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). In all group activation analyses, less than one false positive activation locus was expected for $p < 0.05$ at voxel level and $p < 0.01$ at cluster level.

ANCOVA Between-Group Difference Analyses: For between-group comparisons between controls and patients under either placebo or Fluoxetine, one-way ANCOVA analyses with group as factor and rotational and translation movement in Euclidian 3-D space as covariate, were conducted using randomisation-based tests for voxel or cluster-wise differences as described in detail (Bullmore et al., 1999, Bullmore et al., 2000). For these between-group comparisons, less than 1 false activated cluster was expected at $p < 0.05$ for voxel and $p < 0.01$ for cluster comparisons. Given that right IFC was an apriori hypothesised region, we used a more lenient cluster $p < 0.05$. Then the standardised BOLD response values (SSQ ratios) for each participant were extracted for the mean activation of each of the significant clusters of the 3-group ANCOVA analyses and post-hoc t-tests (correcting for multiple comparisons using least significant difference (LSD)) were conducted to identify the direction of the group differences.

ANCOVA Within-Patients Interaction Effects: In order to investigate group by drug interaction effects between placebo and Fluoxetine within the patient groups, a 2x2 ANCOVA (2 medication conditions, 2 groups) with rotational and translation movement in Euclidian 3-D space as covariate was conducted using randomised-based testing for voxel or cluster-wise differences as described elsewhere (Bullmore et al., 2000). Less than one false positive activation cluster was expected at $p < 0.05$ at voxel and $p < 0.01$ at cluster level. For our apriori hypothesised region in right IFC, a more lenient $p < 0.05$ was used. Statistical measures of BOLD response for each participant were then extracted in each of the significant clusters and post-hoc t-tests (correcting for multiple comparisons with LSD) were conducted to identify the direction of the interaction effects.

Normalisation Effects: To test for the statistical significance of any apparent normalisation effects of Fluoxetine on case-control activation differences observed under placebo, we used non-parametric Friedman two-way analysis of variance by ranks on the extracted BOLD responses during each medication condition for each of the clusters shown to be significantly different in the comparison between controls and patients during placebo. We conducted this test only within patients, given that controls were only tested once, and hence constant across comparisons.

Correlations with Behaviour: To test whether group, or group by drug, interaction effects were related to task performance or clinical behaviour we correlated all clusters with the main inhibitory variable of SSRT as well as with omission errors, since they were lower in ADHD patients relative to controls and ASD, in each group. The SDQ hyperactive/inattentive subscale and CPRS scores in the ADHD group, and the social and communication, and stereotyped behaviours, subscales of the ADOS in the ASD group, were correlated with activation. For this purpose, the BOLD responses in these clusters were extracted for each subject and Pearson correlations were performed between these and performance and behaviour within each group.

6.3 – Results

6.3.1 - Participant Characteristics

Group differences in age and IQ

Univariate ANOVAs showed no significant group differences in age, but did for IQ ($F(df=2,61) = 10, p < 0.001$) which was significantly lower in ADHD relative to control and ASD boys ($p < 0.005$), who did not differ. ADHD children have typically lower IQ than their healthy peers (Bridgett and Walker, 2006). Therefore, we did not covary for IQ, as covarying for a measure that is intrinsic to the condition, and hence differs between groups, that were not randomly selected, would violate ANCOVA assumptions (Dennis et al., 2009). Nonetheless, to assess the potential

impact of IQ on group differences and group by medication interaction effects, analyses were repeated with IQ as covariate.

Group differences in clinical questionnaire measures

Multivariate ANOVA showed a significant group effect for all SDQ measures ($F(df = 10, 112) = 30$, $p < 0.0001$). Post-hoc analyses are shown in the supplement. Post-hoc analyses showed that controls scored significantly better on all subscales compared to patients ($p < 0.001$). ADHD boys scored significantly higher than ASD boys on the conduct and hyperactive/inattentive subscales of the SDQ ($p < 0.0001$) while ASD boys scored significantly worse than ADHD boys on the peer relations and prosocial subscales ($p < 0.05$) and significantly higher on the SCQ than ADHD and controls participants, while ADHD participants scored significantly higher than controls ($F(df = 2, 55) = 152$, $p < 0.0001$). ADHD boys scored higher on the CPRS than ASD and controls and ASD participants scored higher than controls ($F(df = 2, 56) = 192$, $p < 0.0001$) (see Table 4).

Table 4. Sample characteristics for control boys, boys with ADHD and boys with ASD

Variables	Controls (25) Mean (SD)	ADHD (18) Mean (SD)	ASD (19) Mean (SD)
Age (years)	13.4 (2.4)	14.3 (1.8)	14.7 (2.0)
IQ	109 (13)	95 (11)	112 (15)
SDQ Hyperactive/Inattentive Subscale	1.8 (1.6)	9.2 (0.9)	4.5 (1.8)
SDQ - Emotional Distress Subscale	0.5 (0.8)	3.6 (3.0)	4.2 (3.0)
SDQ - Conduct Subscale	0.3 (0.7)	5.0 (2.4)	2.1 (2.0)
SDQ – Peer Relations Subscale	.6 (1.1)	3.4 (2.5)	6.1 (2.4)
SDQ – Prosocial Behaviour Subscale	9.1 (1.3)	6.7 (2.3)	5.1 (2.3)
SDQ – Total scores	3.3 (2.9)	21.2 (4.9)	16.8 (5.7)
SCQ Total	1.6 (2.7)	7.0 (3.4)	23.5 (5.5)
CPRS-R Total T score	44 (3)	83 (7)	57 (8)
ADOS Communication scores	-	-	2 (1)
ADOS Social Interaction scores	-	-	7 (4)
ADOS Social and Communication scores	-	-	9 (5)
ADOS Stereotyped behaviour scores	-	-	1 (1)
ADI Communication scores	-	-	14 (4)
ADI Social Interaction scores	-	-	17 (5)
ADI Stereotyped behaviours scores	-	-	6 (3)

6.3.2 - Performance Data

All subjects achieved a comparable mean probability of inhibition of approximately 50% in the Stop Signal task ($F(df=2,61)=1$ $p=0.3$), demonstrating that the Stop algorithm was successful. ANOVA between controls and patients under placebo showed a significant group effect for omission errors ($F(df=2,61)=4$ $p<0.05$). Post-hoc analysis showed that this was due to the ADHD group making significantly more omission errors than controls ($p < 0.05$) and the ASD group ($p < 0.01$). ANOVA between controls and patients under Fluoxetine showed a significant group effect for omission errors ($F(df=2,61)=5$ $p<0.05$). Post hoc analysis showed that this was due to the ADHD group making significantly more omission errors than controls ($p < 0.05$) and the ASD group ($p < 0.01$) (see Table 5). There were no other significant group differences in performance and no group by medication interaction effects.

Table 5. Performance measures for the Stop Signal task for controls, boys with ADHD and boys with ASD

Performance measure	Controls Mean (SD)	ADHD Placebo Mean (SD)	ADHD Fluoxetine Mean (SD)	ASD Placebo Mean (SD)	ASD Fluoxetine Mean (SD)
SSRT	161 (107)	132 (81)	142 (109)	140 (125)	142 (103)
PI	51	50	49	50	49
MRT to go trials	623 (104)	629 (86)	632 (109)	618 (102)	622 (113)
SD for MRT to go trials	174 (39)	194 (44)	194 (60)	168 (39)	166 (43)
Omission errors	5 (5)	9 (8)*	9 (9)*	3 (5)	3 (3)

Abbreviations: PI = Percentage Inhibition, SSRT = Stop Signal Reaction Time; MRT = Mean Reaction Time (in ms); SD = intrasubject variability of reaction time (in ms); * = ADHD > C, ASD

6.3.3 - fMRI Data

Movement

Repeated measures ANOVAs using group as an independent factor and maximum x, y z rotation and translation as repeated measures showed that there were no significant group by movement interaction effects in rotation ($F(df = 4, 118) = 2$, $p = 0.14$.) or translation ($F(df = 4, 118) = 1$, $p = 0.58$). Nevertheless, to eliminate any potential effects of even small, non-significant variance in motion, motion parameters were used as a covariate in the fMRI analyses.

Group Brain Activation Maps

Successful- Failed Inhibition

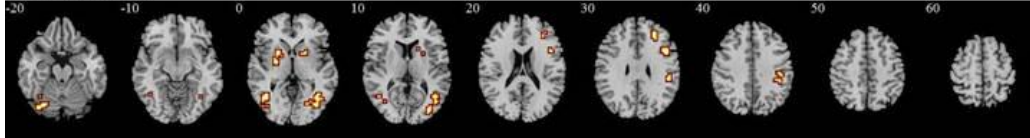
Controls – During successful - failed inhibition controls activated a typical inhibition network consisting of right inferior and middle frontal cortex, right caudate, bilateral putamen/globus pallidus, right middle/superior temporal lobe, right inferior parietal lobe, occipital lobe and left cerebellum.

ADHD – While under placebo, the ADHD group activated bilateral occipital lobe. While under Fluoxetine, they activated right middle and superior frontal cortex, bilateral precentral and postcentral gyri, right caudate, putamen, insula and thalamus, right temporal lobe, bilateral parietal lobe, PCC, bilateral occipital lobe and cerebellum/midbrain.

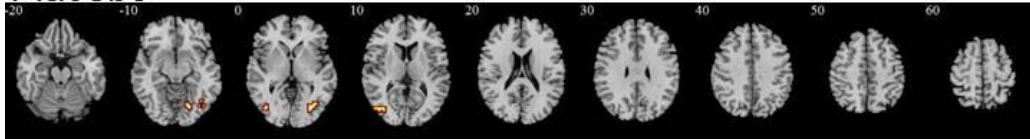
ASD – While under placebo, the ASD group activated bilateral middle and superior frontal cortex, right IFC, right caudate, putamen, thalamus and precuneus, bilateral occipital lobe and cerebellum. While under Fluoxetine, the ASD group activated right precentral and postcentral gyri, right parietal lobe, right middle temporal lobe, bilateral occipital lobe, precuneus and left cerebellum (see Figure 9.A)

Group Brain Activation during Successful – Failed Inhibition

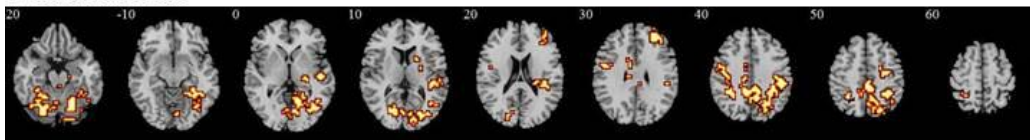
Control



ADHD Placebo

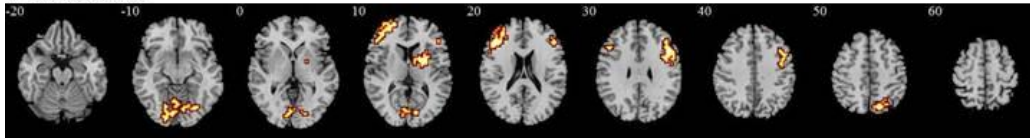


Fluoxetine



ASD

Placebo



Fluoxetine

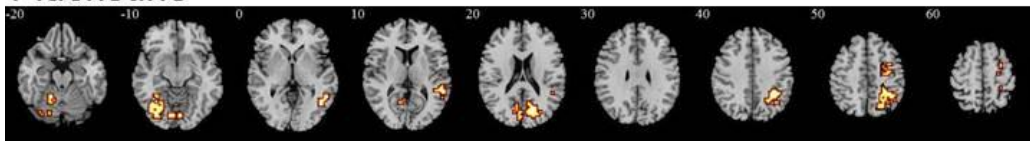


Figure 9.A – Within-group activation for controls, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of successful – failed inhibition. Axial sections showing within-group brain activation for healthy control boys, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of successful – failed inhibition. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image.

Failed - Successful inhibition

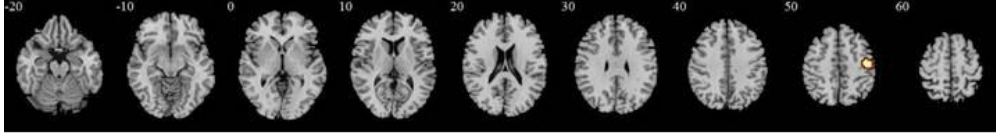
Controls – During failed – successful inhibition controls activated a single cluster in right precentral and postcentral gyri.

ADHD – While under placebo, the ADHD group activated a single cluster in left precentral and postcentral gyri reaching into parietal lobe. While under Fluoxetine, the ADHD group activated mPFC/pre-SMA reaching into left superior frontal cortex and left inferior parietal lobe.

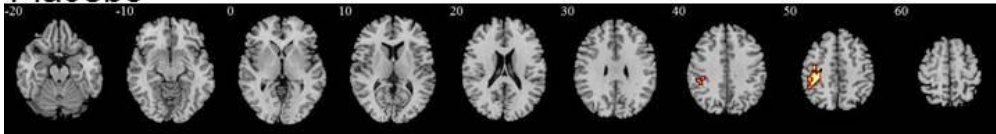
ASD – While under placebo, the ASD group activated mPFC, including ACC, PCC and a left hemispheric network consisting of IFC, post insula, putamen and premotor and postcentral gyri. While under Fluoxetine, they activated ACC and left postcentral gyrus (see Figure 9.B).

Group Brain Activation during Failed – Successful Inhibition

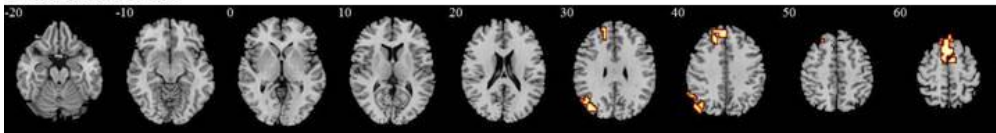
Control



ADHD Placebo

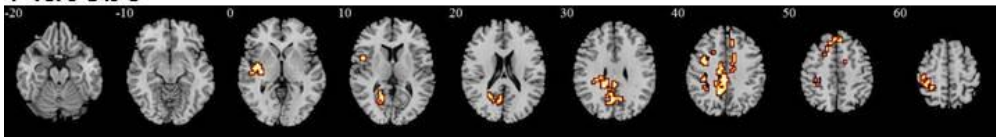


Fluoxetine



ASD

Placebo



Fluoxetine

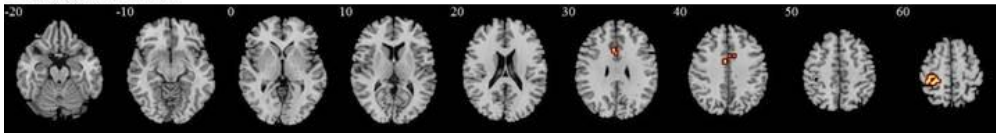


Figure 9.B –Within-group activation for controls, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of failed – successful inhibition. Axial sections showing within-group brain activation for healthy control boys, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of failed – successful inhibition. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image. The right side corresponds to the right side of the image.

Between-group differences between controls and patients under placebo

ANCOVA between controls and patients on placebo showed significant group differences in left middle/IFC, left VLPFC/superior temporal lobe reaching into putamen and globus pallidus, and in left inferior parietal lobe. The right IFC was observed at a more lenient $p < 0.05$ (Figure 10.A, Table 6).

Post-hoc analyses showed that the group effect in right IFC was due to significantly increased activation in this region in the ASD group relative to controls ($p < 0.005$) and trend-wise compared to ADHD boys ($p = 0.08$). In left middle/IFC, the ASD group had significantly increased activation compared to both controls and ADHD participants ($p < 0.005$) who activated this region during failed inhibition and had a trend-wise reduction relative to controls ($p = 0.08$). In left VLPFC/superior temporal lobe/basal ganglia both controls and ASD boys, who did not differ, showed increased activation relative to ADHD boys who activated this area during failed inhibition ($p < 0.005$). Left inferior parietal lobe was significantly reduced in both patient groups relative to controls ($p < 0.05$), with ASD patients activating this area significantly more during failed inhibition than ADHD ($p < 0.05$).

In order to test whether group effects were related to task performance we correlated all clusters with the main inhibitory variable of SSRT as well as with omission errors, since they were lower in ADHD patients relative to controls and ASD. For this purpose, the BOLD responses in these clusters were extracted for each subject and Pearson correlations were performed between these and performance within each group. The (reduced) activation in left VLPFC/basal ganglia in ADHD was significantly negatively correlated with omission errors ($r = -0.506$, $p < 0.05$). No other correlations were significant.

Between-group differences between controls and patients under Fluoxetine

There were significant group differences in left and right pre-SMA/superior frontal cortex, SMA proper, left inferior parietal lobe/middle temporal lobe, right inferior parietal lobe and precuneus (Figure 10.B, Table 6). Post-hoc analyses showed that controls and the ASD group, who did not differ, activated pre-SMA/superior frontal cortex significantly more than ADHD boys who activated this cluster during failed inhibition ($p < 0.0001$). SMA proper was significantly more activated in

patients, who did not differ, relative to controls who activated this region during failed inhibition ($p < 0.05$). In left and right inferior parietal lobe, controls and ASD boys had increased activation relative to ADHD boys who activated this region during failed inhibition ($p < 0.05$). In right inferior parietal lobe, ASD also had increased activation relative to controls ($p < 0.05$). In precuneus, the ADHD group showed significantly enhanced activation relative to both ASD ($p < 0.05$) and controls who activated this region during failed inhibition and differed relative to ASD ($p < 0.05$).

Friedman two-way analysis of variance by ranks showed that Fluoxetine relative to placebo significantly increased activation in left superior temporal lobe/VLPFC/putamen in the ADHD group and in left inferior parietal lobe in the ASD group, as well as reducing activation in right and left IFC in the ASD group, leading to normalisation of these deficits that were observed in patients relative to controls under placebo.

Correlations with performance showed that activation in pre-SMA/superior frontal cortex during successful inhibition was negatively correlated with SSRT in the ASD group ($r = -0.532$, $p < 0.05$). Activation in precuneus was negatively correlated with SSRT in the ADHD group ($r = -0.493$, $p < 0.05$). No other correlations were significant.

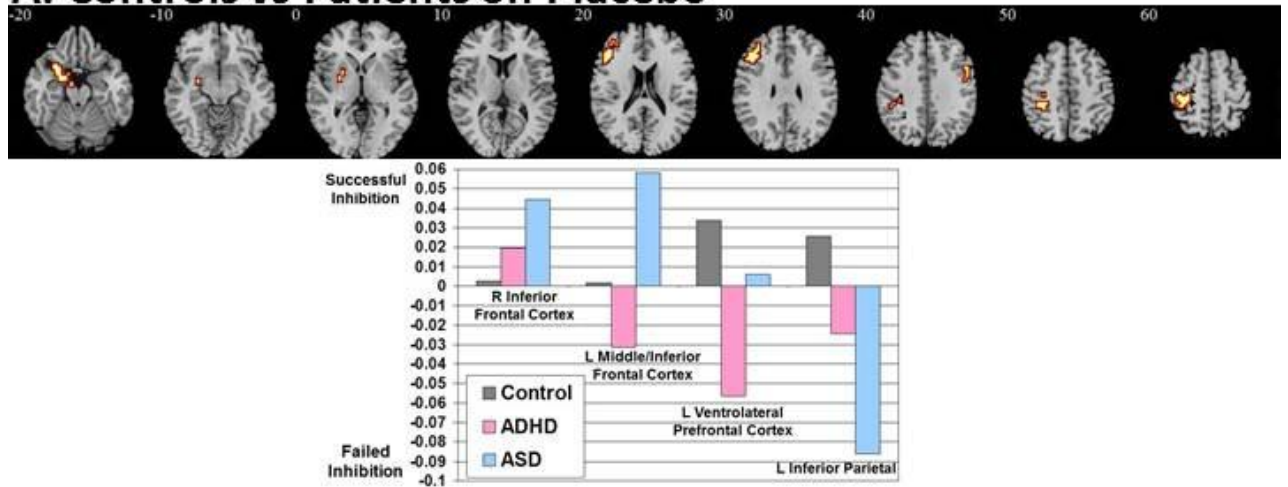
To assess the potential impact of IQ on case-control group differences, all analyses were repeated with IQ as a covariate. All clusters remained at a $p < 0.01$, apart from left VLPFC in the placebo between-group ANCOVA and right inferior parietal lobe in the fluoxetine between-group ANCOVA, which survived at a more lenient $p < 0.05$.

Within-Patients group by medication interaction effects

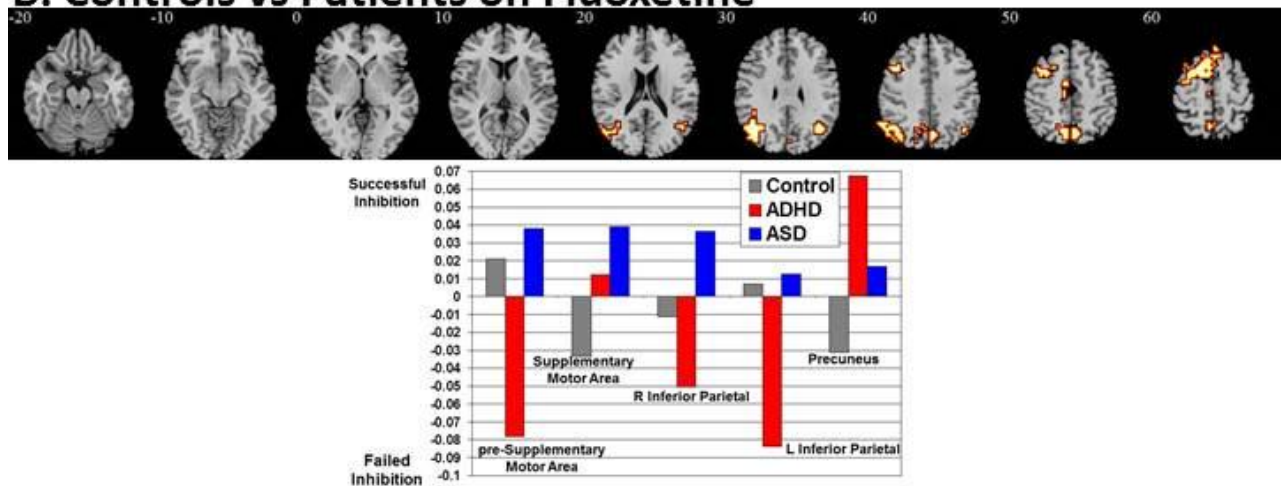
ANCOVA analysis with group as dependent variable and drug as within-group variable showed a significant group by medication interaction effect in five clusters. 1) Fluoxetine reduced pre-SMA activation in the ADHD group, whereas it increased it in the ASD group during successful inhibition ($p < 0.005$). 2) Fluoxetine increased a cluster in left VLPFC/superior temporal lobe/putamen/globus pallidus in ADHD during successful inhibition relative to placebo, but reduced it in ASD ($p < 0.05$). 3) Both patient groups activated left inferior parietal lobe during failed inhibition while on placebo, but the ADHD group activated this region more during failed inhibition and the ASD group more during successful inhibition on Fluoxetine ($p < 0.0001$). 4) Right cerebellum activation was increased under Fluoxetine in ADHD relative to placebo for successful stop trials, while ASD boys activated this area during failed inhibition on both placebo and Fluoxetine ($p < 0.05$). 5) A right IFC cluster was present at a more lenient $p < 0.05$, due to Fluoxetine increasing this activation in ADHD during successful inhibition relative to placebo while decreasing it in the ASD group relative to placebo ($p < 0.05$) (Figure 10.C, Table 7). No significant correlations with performance were observed. All findings remained significant at $p < 0.01$ when IQ was covaried for.

Between-Group Comparisons

A. Controls vs Patients on Placebo



B. Controls vs Patients on Fluoxetine



Within-Patient Comparisons

C. Group by Medication Interaction Effects

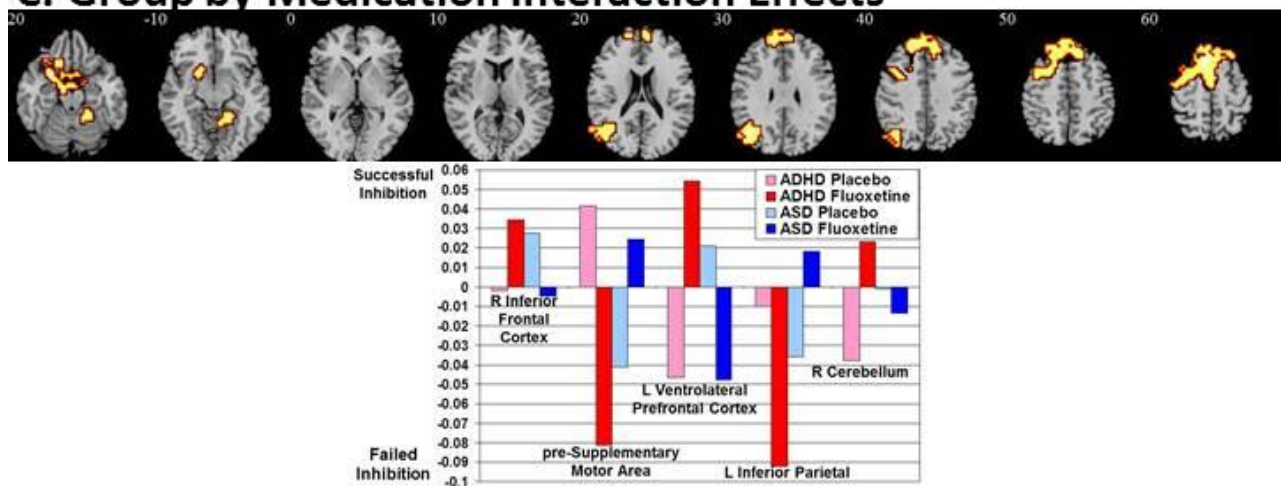


Figure 10.A Stop Signal Task Between-Group and Within-Patient Comparisons:

Axial sections showing the between-group ANCOVA findings between controls and patients under placebo. Shown underneath are the statistical measures of BOLD response for each of the 3 groups for each of the brain regions that showed a significant group effect. **B.** Axial sections for the between-group ANCOVA comparison between controls and patients under Fluoxetine. Shown underneath are the statistical measures of BOLD response for each of the 3 groups for each of the brain regions that showed a significant group effect. **C.** Axial sections showing within-patient group by medication interaction effects. Shown underneath are the statistical measures of BOLD response for each of the brain regions that showed a significant group by medication interaction effect between patients. Talairach z coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 6. Brain activation differences during motor response inhibition between controls and patients on placebo or Fluoxetine

Post-Hoc Group Differences	Brain regions of activation differences	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p-value
PLACEBO					
C < ASD	R Inferior frontal cortex	44	54;15;26	16	0.03
C, ADHD < ASD	L Inferior/middle frontal cortex	44/45/46/9	-40;30;23	82	0.002
C, ASD > ADHD	L Superior temporal lobe/VLPFC/putamen/globus pallidus	38/47/11/25	-29;11;-26	73	0.008
C > ADHD > ASD	L Inferior parietal lobe	40	-29;-22;40	97	0.002
FLUOXETINE					
C, ASD > ADHD	L + R pre-SMA/premotor/superior frontal cortex	6/8 6/8/9	-11;4;63	203	0.0006
C < ADHD, ASD	SMA proper	6	-4;-11;50	42	0.007
ADHD < C < ASD	R Inferior parietal lobe/angular gyrus	40/39	36;-63;30	50	0.004
C, ASD > ADHD	L Inferior parietal lobe/middle temporal	40/39	-47;-63;26	188	0.0002
C < ASD < ADHD	Precuneus	19/7	7;-67;43	114	0.002

Table 7. Group by drug interaction effects within ADHD and ASD patients during motor response inhibition

Brain regions of activation	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p-value
R Inferior/middle frontal cortex	44/9	51;0;26	21	0.03
R pre-SMA/premotor/superior frontal cortex	6/8	-7;33;56	1085	0.0003
L Superior temporal lobe/VLPFC/putamen/globus pallidus	38/47/11/25	-4;-7;-26	452	0.004
L Inferior parietal/middle/superior temporal lobe/occipital lobe	39/40/22/19	-43;-67;30	237	0.008
R Cerebellum		22; -41; -17	139	0.0005

6.4 – Discussion

This study shows inverse brain dysfunction patterns in inhibitory brain regions in ADHD and ASD as well as inverse disorder-dissociated modulation effects of Fluoxetine on these neurofunctional abnormalities. Relative to controls, ADHD patients showed reduced left VLPFC/basal ganglia activation whereas ASD patients showed enhanced left and right IFC activation relative to ADHD and controls. Fluoxetine significantly normalised these disorder-dissociated brain abnormalities relative to controls, via disorder-dissociated inverse effects within patients: Fluoxetine enhanced the abnormally reduced VLPFC/basal ganglia activation in ADHD, but reduced it in ASD. In contrast, it reduced the abnormally enhanced IFC activation in ASD, but enhanced it in ADHD. Furthermore, Fluoxetine also inverse disorder-dissociated effects on other inhibition areas such as pre-SMA and cerebellum: these were, respectively, enhanced (SMA) and reduced (cerebellum) in ADHD with Fluoxetine relative to placebo, but reduced (SMA) and enhanced (cerebellum) in ASD.

The finding of disorder-specific increased activation in ASD relative to controls and ADHD in left IFC and in right IFC (where it was only trend-wise different to ADHD) extends our previous finding of increased left IFC activation in young adults with Asperger syndrome compared to controls during a Go/No-Go task (Schmitz et al., 2006) by showing that this hyperactivation is disorder-specific relative to ADHD. Predominantly right (Rubia et al., 2003) but also left IFC (Rubia et al., 2001a) are crucial areas mediating response inhibition. ADHD patients had no underactivation in these areas relative to controls as observed previously (Rubia et al., 1999, Rubia et al., 2005b), but did relative to ASD. Potential practice effects (may have overshadowed deficits in both IFC activation and inhibitory performance since ADHD patients performed the task twice. The deficits in ADHD adolescents in left VLPFC/basal ganglia relative to controls extends prior findings of VLPFC-striatal deficits in ADHD (Rubia et al., 1999, Rubia et al., 2005b, Hart et al., 2012b) (albeit in a more ventral location). Therefore, our results show disorder-dissociated frontal lobe dysfunctions in ADHD and ASD boys during inhibitory performance relative to controls: with ASD patients showing significantly enhanced bilateral IFC activation and ADHD boys showing significantly reduced VLPFC/basal ganglia activation.

Fluoxetine significantly normalised all disorder-dissociated frontal brain dysfunctions due to inverse modulation effects in both disorders. Fluoxetine significantly reduced right IFC and left VLPFC activation in the ASD group but enhanced it in ADHD. Fluoxetine also had an inverse upregulation/downregulation effect on another key inhibition region of pre-SMA: this was upregulated in ASD and hence increased relative to controls and ADHD, but downregulated in ADHD and hence reduced relative to controls and ASD. The upregulation effect of Fluoxetine on right IFC and VLPFC-striatal regions in ADHD extends prior evidence on 5-HT modulation of these areas in healthy adults during inhibitory control (Del-Ben et al., 2005) to the ADHD population. Most intriguing, however, are the consistently inverse reduction effects of Fluoxetine on these frontal activations in the ASD group. Inverse activation effects could possibly reflect group differences in baseline 5-HT levels. There is evidence for lower platelet 5-HT levels in ADHD children compared to controls (Spivak et al., 1999). Conversely, there is consistent evidence for increased baseline platelet and blood 5-HT levels in 30% of individuals with ASD (Hranilovic et al., 2007) and in prefrontal regions, relative to controls (Nakamura et al., 2010).

Furthermore, during emotion processing, serotonergic modulation with ATD in adults with ASD compared to controls has shown inverse patterns of neurofunctional modulation, suggesting abnormal 5-HT baseline levels in ASD (Daly et al., 2012). Therefore, Fluoxetine may increase the low baseline of 5-HT in children with ADHD to normal levels, leading to normalised activation in fronto-striatal areas. Whereas in children in ASD, the increase in 5-HT in an already hyperserotonemic system may activate a negative feedback mechanism via activation of 5-HT_{1A} autoreceptors (Sibley et al., 2007), leading to a decrease in 5-HT and in fronto-striatal activation.

A limitation of this study is that the control group was only scanned once, while patients were scanned twice which could have accounted for the lack of performance differences. The significantly lower IQ in the ADHD group is another limitation. However, covariance analysis showed that findings were not affected by IQ. The strengths of this study are the carefully selected and non-comorbid patient

groups who were free of psychiatric co-morbidities and, in the case of the ASD group, medication naïve.

To summarise, ADHD and ASD patients showed inverse brain activation abnormalities, with reduced frontal activations in ADHD and enhanced frontal activation in ASD relative to controls. Importantly, Fluoxetine had a disorder-dissociated inverse effect on frontal brain dysfunctions, enhancing frontal activation in ADHD and reducing it in ASD which could suggest differential underlying 5-HT baseline levels in the two disorders.

Chapter 7 – Inverse effect of Fluoxetine on medial prefrontal cortex activation during reward reversal learning in ADHD and ASD

7.1 – Introduction

ADHD is a neurodevelopmental disorder characterized by age-inappropriate levels of impulsiveness, inattention and hyperactivity (American et al., 1994). ASD is also a neurodevelopmental disorder, and is defined by impairments in communication and social interaction, as well as restricted and repetitive behaviours (American et al., 1994). ADHD and ASD are highly comorbid with recent studies reporting an overlap of up to 30% (Simonoff et al., 2008, Kochhar et al., 2011, Rommelse et al., 2011). However, the underlying cause of this high risk for co-morbidity, and the shared and disorder-specific biological profiles of these disorders, are still unknown. Both disorders share executive function deficits (Willcutt et al., 2005, Rommelse et al., 2011, Corbett et al., 2009) including poor cognitive flexibility (Hill, 2004, Willcutt et al., 2005, Sanders et al., 2008) which has been linked to repetitive behaviours in ASD (Yerys et al., 2009). The clinical importance of this behavioural and cognitive overlap has been highlighted by changes to the upcoming DSM-V which allows co-diagnosis of both ADHD and ASD (<http://www.dsm5.org>).

Cognitive flexibility can be measured in switching and reversal tasks, where stimulus-response associations need to be either changed to new, or reversed to previous stimulus-response associations, respectively. fMRI studies of switch tasks have found decreased activation in ADHD compared to controls in IFC, the temporo-parietal junction and striatum (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a, Hart et al., 2013), and reversal studies have found abnormal medial frontal and precuneus activation (Finger et al., 2008). No fMRI study has investigated cognitive flexibility in ASD children, with two adult ASD studies reporting conflicting evidence of decreased activation in DLPFC, ACC and basal ganglia (Shafritz et al., 2008), and increased activation in IFC and parietal lobe relative to controls (Schmitz et al., 2006).

There is evidence that manipulation of 5-HT modulates reward reversal learning (Roberts, 2011, Murphy et al., 2002, Evers et al., 2005). Polymorphisms of serotonergic genes have been associated with both ADHD and ASD (Rommelse et al., 2010, Sinzig and Lehmkuhl, 2007) and there is evidence that a polymorphism of the 5-HT_{1A} receptor may play a role in the ADHD symptoms observed in ASD (Gadow et al., 2013). Furthermore, biochemical serotonergic dysfunction has been implicated in both ADHD (Oades, 2007) and ASD (Zafeiriou et al., 2009), with evidence for decreased platelet 5-HT levels in ADHD (Spivak et al., 1999) and increased platelet 5-HT levels in one third of individuals with ASD (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007). In ASD abnormal 5-HT synthesis (Chugani et al., 1999, Chugani et al., 1997), SERT binding (Makkonen et al., 2008, Nakamura et al., 2010) and 5-HT_{2A} receptor binding (Murphy et al., 2006) has also been reported. Fluoxetine has been shown to increase metabolic and neurofunctional activity in adults with ASD in areas mediating reward reversal learning such as OFC and mPFC, ACC and striatum (Mitchell et al., 2008, Freyer et al., 2009), which was associated with reduced obsessive behaviour (Buchsbaum et al., 2001, Dichter et al., 2010). Clinical trials of Fluoxetine in children with ASD have shown improvement in communication, social interaction and stereotyped behaviours (DeLong et al., 2002, DeLong et al., 1998, Hollander et al., 2005, Carrasco et al., 2012), although effects are small (Williams et al., 2010) and studies using Citalopram have found no effects (King et al., 2009). In children with ADHD, Fluoxetine has been shown to improve irritability, inattentiveness and hyperactivity (Gammon and Brown, 1993, Barrickman et al., 1991, Quintana et al., 2007).

Despite the cognitive and neurofunctional evidence for impaired cognitive flexibility in ADHD (Willcutt et al., 2005, Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a, Finger et al., 2008) and ASD (Hill, 2004, Sanders et al., 2008, Shafritz et al., 2008, Schmitz et al., 2006), for 5-HT abnormalities in both disorders (Rommelse et al., 2010, Sinzig and Lehmkuhl, 2007, Gadow et al., 2013, Oades, 2007, Zafeiriou et al., 2009, Spivak et al., 1999, Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007, Chugani et al., 1999, Chugani et al., 1997, Makkonen et al., 2008, Nakamura et al., 2010, Murphy et al., 2006, Buchsbaum et al., 2001, Dichter et al., 2010), the positive effect of 5-HT upregulation on cognitive flexibility (Roberts, 2011) and the ameliorative effect of Fluoxetine on behaviour in these two

disorders (DeLong et al., 2002, DeLong et al., 1998, Hollander et al., 2005, Carrasco et al., 2012, Gammon and Brown, 1993, Barrickman et al., 1991, Quintana et al., 2007), no study has as yet compared the shared and disorder-specific neurofunctional abnormalities of this executive function, nor the modulatory effects of Fluoxetine.

The aim of this fMRI study was therefore to investigate 1) shared and disorder-specific brain abnormalities in adolescents with ADHD and adolescents with ASD during reward reversal learning and 2) shared and disorder-specific neurofunctional effects of an acute dose of Fluoxetine on this function in both disorders. Based on prior evidence (Smith et al., 2006, Rubia et al., 2010a, Rubia et al., 2010b, Hart et al., 2013, Shafritz et al., 2008) we hypothesised that under placebo, both disorders would show abnormal activation in IFC, mPFC and striatum compared to controls, with disorder-dissociated abnormalities in these regions. We hypothesised that Fluoxetine would normalise these neurofunctional abnormalities in both disorders.

7.2 - Methods

7.2.1 – Participants

Thirty - two ADHD boys were recruited in total, however; 10 dropped out of the study due to their dislike of the MRI scanner, three were excluded due to co-morbidities, one boy did not reach the diagnostic criteria for the combined subtype of ADHD, one boy was excluded due to poor task performance and two were excluded due to high levels of motion. Forty - four ASD boys were recruited in total. Of these, seven boys dropped out of the study due to their dislike of the MRI scanner, 14 were excluded due to co-morbidities, one was excluded due to neurological abnormalities, two were excluded due to SSRI use and two were excluded due to high levels of motion. Twenty - two controls were recruited in total however one was excluded due to high scores on the SDQ.

Fifty-four right handed males (assessed with the Edinburgh Handedness Inventory) (Oldfield, 1971) (21 controls, 15 with ADHD and 18 with ASD) aged 10-

17 years old, with an IQ > 70 (assessed with the Wechsler Abbreviated Scale of Intelligence-Revised (Wechsler, 1999) participated.

ADHD boys met the diagnostic DSM-IV criteria for hyperactive-impulsive/inattentive combined type ADHD and scored above clinical threshold for ADHD on both the SDQ (Goodman and Scott, 1999) and the CPRS (Conners et al., 1998) (one boy was below cut-off on SDQ but had diagnostic confirmation from a child psychiatrist). Three ADHD boys were medication-naïve, one ceased taking MPH for three months prior to the study and 11 were on chronic stimulants, but all had a 48hr medication washout prior to scanning.

ASD diagnosis was made using ICD-10 diagnostic criteria (World et al., 1994) and confirmed by the ADI-R (Lord et al., 1994) and the ADOS (Lord et al., 2000). All ASD subjects were medication-naïve apart from one patient, who took melatonin, but underwent two week medication washout. ASD exclusion criteria included a score above seven on the hyperactivity/inattention subscale of the SDQ. ADHD boys were excluded if they scored above 15 on the SCQ (Rutter et al., 2003). Comorbidity with other psychiatric or neurological disorders and drug/alcohol dependency were exclusion criteria for all patients. Patients were recruited from local clinical services and support groups. Written informed consent/assent was given for all participants and the study was approved by the local Ethical Committee.

Patients were scanned twice in a double-blind, randomised, placebo-controlled design, using a Latin square randomisation design for counter-balanced effects. Due to the half-life of Fluoxetine, (1-3 days), and its metabolite Norfluoxetine (5-16 days) (Wong et al., 1995) each scan was 3-4 weeks apart. To ensure that Fluoxetine had reached its peak plasma levels, which occur after 5-8 hours (Wong et al., 1995), patients were scanned five hours after administration. Liquid Fluoxetine was titrated to age and weight in the following manner. Boys between 10-13 years and less than 30kg received 8mg, those greater than 30kg received 10mg. Boys between 14-17 years and less than 30kg received 10mg, those greater than 30kg received 15mg. Placebo was equivalent amounts of peppermint water which was similar in taste to Fluoxetine.

Twenty-one age and handedness matched control boys were recruited locally by advertisement. They all scored below clinical thresholds on the SDQ, SCQ and CPRS.

7.2.2 - fMRI Reward Reversal Learning Paradigm

Subjects practised the task once prior to each scan. Our fMRI adaptation is similar to the probabilistic reward reversal learning task employed by Cools et al 2002 (Cools et al., 2002). The semi self-paced reward reversal learning task requires subjects to reverse their response and select a previously unrewarded stimulus after learning a particular stimulus-reward association. Images of a car and a spaceship are displayed simultaneously on the left and right side (randomised) of a black screen for 1950ms, and the subject has to choose the correct choice with a left and right button press, indicated by feedback which is a photo of a 50 pence piece and a green happy smiley. The incorrect choice is indicated by a photo of a crossed-out 50 pence piece and a red unhappy smiley, both displayed after the choice for 950ms. There is a 100ms gap between each trial leading to an inter-trial interval of 3s. Reversal of the stimulus-reward association occurs after 4-6 consecutive correct responses, allowing adequate separation of the haemodynamic response curves. The task ends after 20 reversal trials or after 20 minutes, whichever condition is met first. Zero to 2 probabilistic error trials (PET), where negative feedback is given for a correct response, are randomly interspersed between reversal trials to prevent subjects from predicting an upcoming reversal trial. PET trials are at least 3 trials apart from other PETs and reversal trials for adequate separation of haemodynamic response curve (Figure 11). The main dependent variable of this task is the number of perservative errors made after a reversal trial.

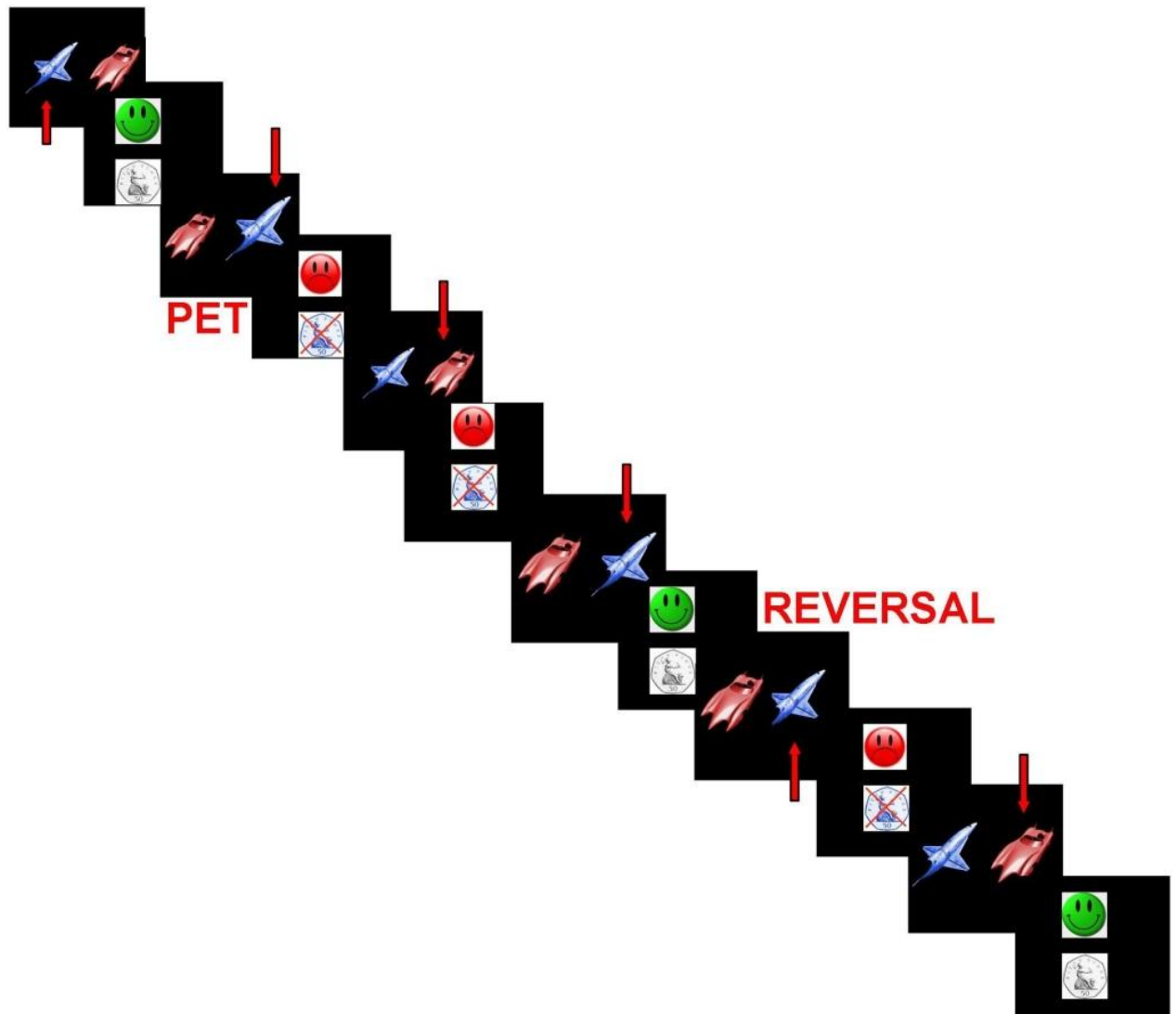


Figure 11 – Reward Reversal Learning Task: Subjects select an image (right/left) by pressing the corresponding button (right/left). If the choice is correct/incorrect, positive/negative feedback is given. Once the subject has made 4-6 correct responses, the stimulus reward contingency is reversed. Probabilistic Error Trials (PET), where incorrect feedback is given for a correct response, are included to prevent subjects from predicting an upcoming reversal trial. The task contains on average 20 reversal trials with 20 interspersed PET trials.

7.2.3 - Data Analysis

Analysis of performance data

Two ANOVAs compared perseverative errors between controls and patients under either placebo or Fluoxetine. A repeated-measures ANOVA was conducted within the patient groups with group as an independent factor and drug (placebo/Fluoxetine) as a repeated measure to test for group by medication interaction effects on performance.

fMRI Image acquisition

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a General Electric Signa 3T Horizon HDx system at the Centre For Neuroimaging Sciences, Institute of Psychiatry, King's College London, UK. A semi-automated quality control procedure ensured consistent image quality (Simmons et al., 1999). A quadrature birdcage headcoil was used for radio frequency transmission and reception. In each of 23 non-contiguous planes parallel to the anterior-posterior commissure, 800 T2*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with TE=30ms, TR=1.5s, flip angle=70°, in-plane voxel size=3mm, slice thickness=5.5mm (including slice-skip=0.5mm). This EPI dataset provided almost complete brain coverage. A whole-brain high resolution structural scan (inversion recovery gradient echo planar image) on which to superimpose the individual activation maps, was also acquired in the inter-commissural plane with TE=30 ms, TR=3s, flip angle = 90°, 43 slices, slice thickness=3.0mm, slice skip=0.3mm, in-plane voxel-size = 1.875mm.

fMRI image analysis

The XBAM software package was used (<http://www.brainmap.co.uk>) (Brammer et al., 1997) which makes no normality assumptions (often violated in fMRI data), but instead uses median statistics to control outlier effects and permutation rather than normal theory-based inference (Thirion et al., 2007). In the fMRI analysis, brain activation to PETs are subtracted from brain activation to the final reversal error before a correct response. This stringent contrast captures the point at which subjects learn to reverse their response, and controls for the brain response to the punishment given in the negative feedback in both trials. This contrast has been

used in previous fMRI studies of reward reversal learning (Cools et al., 2002, Remijne et al., 2005).

Individual Analysis: fMRI data were first processed to minimise motion related artifacts (Bullmore et al., 1999). A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the x y and z axes) and translations (in x y and z) that maximised the correlation between the image intensities of the volume in question and the template (rigid body registration). Following realignment, data were then smoothed using a Gaussian filter (FWHM, 7.2mm) to improve the signal to noise characteristics of the images. After preprocessing, time series analysis for each subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore et al., 2000, Bullmore et al., 1999). At the individual subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to the reward reversal task condition final reversal error against probabilistic error trials. Briefly, we first convolved the main experimental conditions (final reversal error versus repeat trials; probabilistic error trials versus repeat trials) with two Poisson model functions (peaking at 4s and 8s) after motion correction, global detrending and spin-excitation history correction. We also calculated the difference between the two (i.e. final reversal error versus probabilistic error trials). We then calculated the weighted sum of these two convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (the SSQ-ratio) was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ-ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2000) and applying the model-fitting process to the re-sampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ-ratio for each subject, which were combined to give the overall null distribution of SSQ-ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation

structure in the data. Activated voxels, at a <1 level of type I error, were identified through the appropriate critical value of the SSQ-ratio from the null distribution. Individual SSQ-ratio maps were then transformed into standard space, first by rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

Group Analysis: A group activation map was produced for the key experimental condition (final reversal error – probabilistic error trials) by calculating the median observed SSQ-ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ-ratios computed from the identically transformed wavelet re-sampled data (Brammer et al., 1997). The voxel-level threshold was first set to 0.05 to give maximum sensitivity and to avoid type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each data set, giving excellent Type II error control (Bullmore et al., 1999). Cluster mass rather than a cluster extent threshold was used, to minimise discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999). In all group activation analyses, less than one false positive activation locus was expected for $p < 0.05$ at voxel level and $p < 0.01$ at cluster level.

ANCOVA Between-Group Difference Analyses: For the between-group comparisons between controls and patients under either placebo or Fluoxetine, one-way ANCOVA analyses, with group as an independent factor and rotational and translation movement in Euclidian 3-D space as a covariate, were conducted using randomisation-based tests for voxel or cluster-wise differences as described in detail elsewhere (Bullmore et al., 2000, Bullmore et al., 1999). For these between-group comparisons, a p-value of $p < 0.05$ was used for voxel and $p < 0.02$ for cluster comparisons to achieve an optimal balance between type II and type I error. Then the standardised BOLD response values (SSQ ratios) for each participant were extracted for each of the significant clusters of the 3-group ANCOVA analyses and post-hoc t-tests (correcting for multiple comparisons using least significant difference (LSD)) were conducted to identify the direction of the between-group differences.

ANCOVA Within-Patient Interaction Effects: In order to investigate the group by drug interaction effects between placebo and Fluoxetine within-patient groups, a 2x2 ANCOVA (2 medication conditions, 2 groups) with rotational and translation movement in Euclidian 3-D space as covariate was conducted using randomisation-based testing for voxel or cluster-wise differences as described elsewhere (Bullmore et al., 2000). Less than one false positive 3D cluster was expected at $p < 0.05$ at voxel level and $p < 0.01$ at the cluster level. Statistical measures of BOLD response for each participant were then extracted in each of the significant clusters and post-hoc t-tests (correcting for multiple comparisons with LSD) were conducted to identify the direction of the interaction effects.

Normalisation Effects: To test for the statistical significance of any apparent normalisation effects of Fluoxetine on case-control activation differences observed under placebo, we used non-parametric Friedman two-way analysis of variance by ranks on the extracted BOLD responses during each medication condition for each of the clusters shown to be significantly different in the comparison between controls and patients during placebo. We conducted this test within patients only, given that controls were tested once.

Correlations with Behaviour: To test whether group, or group by drug, interaction effects were related to task performance or clinical behaviour we correlated all clusters with perservative errors in each group. The SDQ hyperactive/inattentive subscale and CPRS scores in the ADHD group, and the social and communication, and stereotyped behaviours, subscales of the ADOS, and the social interaction subscale of the ADI, in the ASD group, were correlated with activation. For this purpose, the BOLD responses in these clusters were extracted for each subject and Pearson correlations were performed between these and performance and behaviour within each group.

7.3 – Results

7.3.1 - Participant Characteristics

Group Differences in age and IQ

ANOVAs showed no significant group differences in age, but did for IQ ($F(df = 2, 53) = 7, p < 0.002$), which was significantly lower in ADHD relative to control and ASD boys ($p < 0.005$), who did not differ from each other. ADHD children typically have lower IQ than their healthy peers (Bridgett and Walker, 2006). Therefore, IQ was not covaried, as when the covariate is intrinsic to the condition, and differs between groups who were not randomly selected, it violates ANCOVA assumptions (Dennis et al., 2009). Nonetheless, to assess the potential impact of IQ on group differences and group by medication interaction effects, the analyses were repeated with IQ as covariate.

Group Differences in clinical questionnaires

Multivariate ANOVA showed a significant group effect for all SDQ measures ($F(df = 10, 94) = 18, p < 0.0001$). Post-hoc analyses showed that controls scored significantly better on all subscales compared to patients ($p < 0.05$), apart from the conduct subscale where ASD boys scored equally as low as controls. ADHD boys scored significantly higher than ASD boys on the conduct and hyperactive/inattentive subscales of the SDQ ($p < 0.005$), while the ASD boys scored significantly worse than the ADHD boys on the peer relation subscale ($p < 0.0001$). ASD boys scored significantly higher on the SCQ than ADHD and controls participants, while ADHD participants scored significantly higher than controls ($F(df = 2, 50) = 134, p < 0.0001$). ADHD boys scored higher on the CPRS than ASD and controls participants and the ASD participants scored higher than controls ($F(df = 2, 51) = 126, p < 0.0001$) (Table 8).

Table 8. Sample characteristics for control boys, boys with ADHD and boys with ASD

Variables	Controls (21) Mean (SD)	ADHD (15) Mean (SD)	ASD (18) Mean (SD)
Age (years)	14.2 (2.6)	14.6 (1.8)	14.6 (1.9)
IQ	107 (14)	96 (12)	114 (16)
SDQ Hyperactive/Inattentive Subscale	2.9 (1.8)	8.9 (1.4)	4.8 (1.6)
SDQ - Emotional Distress Subscale	0.8 (1.4)	3.1 (3.2)	4.3 (3.0)
SDQ - Conduct Subscale	1.0 (1.7)	4.4 (2.3)	2.1 (2.0)
SDQ – Peer Relations Subscale	1.2 (1.1)	3.1 (2.2)	6.3 (2.4)
SDQ – Prosocial Behaviour Subscale	8.6 (1.7)	6.3 (2.3)	5.1 (2.3)
SDQ – Total scores	5.9 (3.9)	19.5 (5.1)	17.6 (5.3)
SCQ Total	2.1 (2.9)	7.2 (3.8)	23.8 (5.3)
CPRS-R Total T score	44 (3)	82 (7)	58 (8)
ADOS Communication scores	-	-	2 (1)
ADOS Social Interaction scores	-	-	7 (4)
ADOS Social and Communication scores	-	-	10 (5)
ADOS Stereotyped behaviour scores	-	-	1 (1)
ADI Communication scores	-	-	15 (4)
ADI Social Interaction scores	-	-	17 (5)
ADI Stereotyped behaviour scores	-	-	5 (3)

7.3.2 - Performance Data

ANOVA between controls and patients under placebo showed no significant group effect ($F(df = 2, 53) = 2, p = 0.170$), although both patient groups made numerically more errors with a relatively large effect size of 0.12 for ADHD and a medium effect size of 0.05 for ASD. Fluoxetine showed a significant group effect for perseverative errors ($F(df = 2, 53) = 4, p < 0.05$) which were significantly higher in ADHD relative to controls ($p < 0.005$). (Mean perseverative errors: Controls: 1.4 (SD = 0.3); ADHD placebo: 1.7 (SD = 0.5); ADHD Fluoxetine: 1.8 (SD = 0.4); ASD placebo: 1.7 (SD = 0.6); ASD Fluoxetine: 1.6 (0.4)). There were no group by medication interaction effects.

7.3.3 - fMRI Data

Movement

Repeated measures ANOVAs using group as an independent factor and maximum x, y and z rotation or maximum x, y and z translation as repeated measures showed that there were no significant group by movement interaction effects in rotation ($F(df = 4, 102) = 2, p = n.s.$) or translation ($F(df = 4, 102) = 2, p = n.s.$). Nevertheless, to eliminate any potential effects of non-significant variance in motion, motion parameters were used as covariates in fMRI analysis.

Group Brain Activation Maps

Final Reversal Error – Probabilistic Error

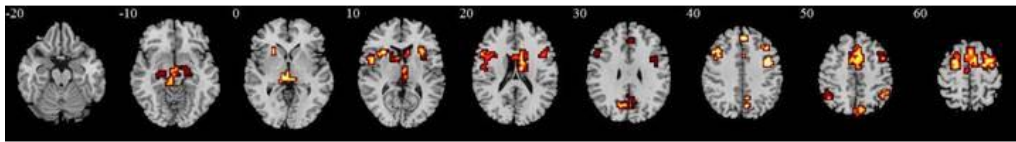
Control – At the point of deciding to reverse their response compared to probabilistic errors, control activated mPFC, SMA, ACC, and a bilateral network involving precentral/postcentral gyri, inferior/middle/superior frontal cortices, basal ganglia, thalamus, midbrain and PCC/precuneus,

ADHD – Under placebo, at the point of deciding to reverse their response, ADHD subjects activated mPFC/ACC, left precentral/postcentral gyri, right middle frontal cortex, bilateral IFC/insula, putamen and left inferior, and right superior, parietal cortices. Under Fluoxetine, ADHD subjects activated SMA, left superior parietal lobe and right hippocampal gyrus.

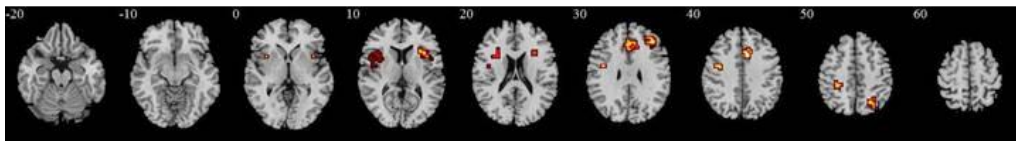
ASD – Under placebo, at the point of deciding to reverse their response, ASD subjects activated bilateral IFC/caudate/putamen and a right hemispheric network comprising precentral/postcentral gyrus, inferior/superior parietal lobe, precuneus and fusiform gyrus/cerebellum. Under Fluoxetine, ASD subjects activated a right hemispheric network consisting of middle/superior frontal cortex, superior parietal lobe and precuneus (Figure 12).

Group Brain Activation during Final Reversal Error – Probabilistic Error

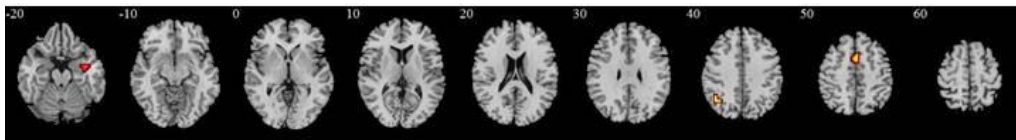
Control



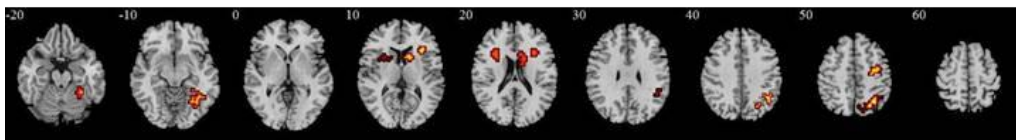
ADHD Placebo



Fluoxetine



ASD Placebo



Fluoxetine

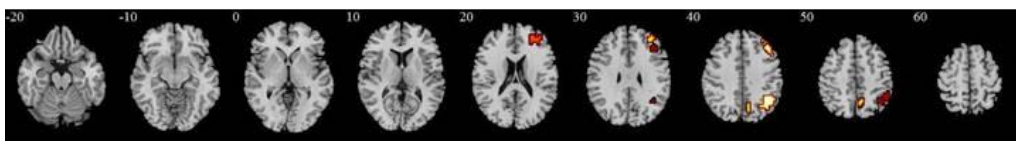


Figure 12– Within-group activation for controls, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of Final Reversal Error – Probabilistic Error. Axial sections showing within-group brain activation for healthy control boys, boys with ADHD under either placebo or Fluoxetine and boys with ASD under either placebo or Fluoxetine for the contrast of final reversal error – probabilistic error. Talairach z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side corresponds to the right side of the image.

Between-Group differences between controls and patients under placebo

ANCOVA between controls and patients under placebo showed significant group effects in mPFC and precuneus reaching into PCC (Figure 13.A Table 9). Post-hoc analyses showed that the group effect in mPFC was due to significantly decreased activation in ASD compared to controls ($p < 0.0001$) and ADHD ($p < 0.0001$), who did not differ from each other. In precuneus both ADHD ($p < 0.005$) and ASD ($p < 0.05$) groups, who did not differ from each other, had significantly decreased activation compared to controls.

In order to test whether group effects were related to performance or behaviour we correlated the statistical BOLD response in group difference clusters with perseverative errors and behavioural scores within each group. For this purpose, the statistical BOLD response measures in these clusters were extracted for each subject and Pearson correlations were performed between these, performance and behavioural scores. The activation in precuneus in ASD was positively correlated with perseverative errors ($r = 0.5$, $p < 0.05$). No other correlations were significant.

Between-Group differences between controls and ADHD and ASD patients under Fluoxetine

ANCOVA between controls and patients under Fluoxetine showed a significant group effect in left insula reaching into putamen (Figure 13.B, Table 9). Post-hoc analyses showed that this difference was due to significantly reduced activation in the ASD group compared to controls ($p < 0.005$), who did not differ from ADHD.

Friedman two-way ANOVA by ranks showed a significant effect of drug condition in mPFC $\chi^2 (1, N=18) = 5.56$, $p < 0.05$) which was due to significantly increased activation in mPFC in the ASD group under Fluoxetine relative to placebo. No other significant normalisation effects were observed.

Correlation analyses showed that the (reduced) activation in left insula in ASD was negatively correlated with scores on the social domain of the ADI ($r = -0.5$, $p < 0.05$). No other correlations were significant.

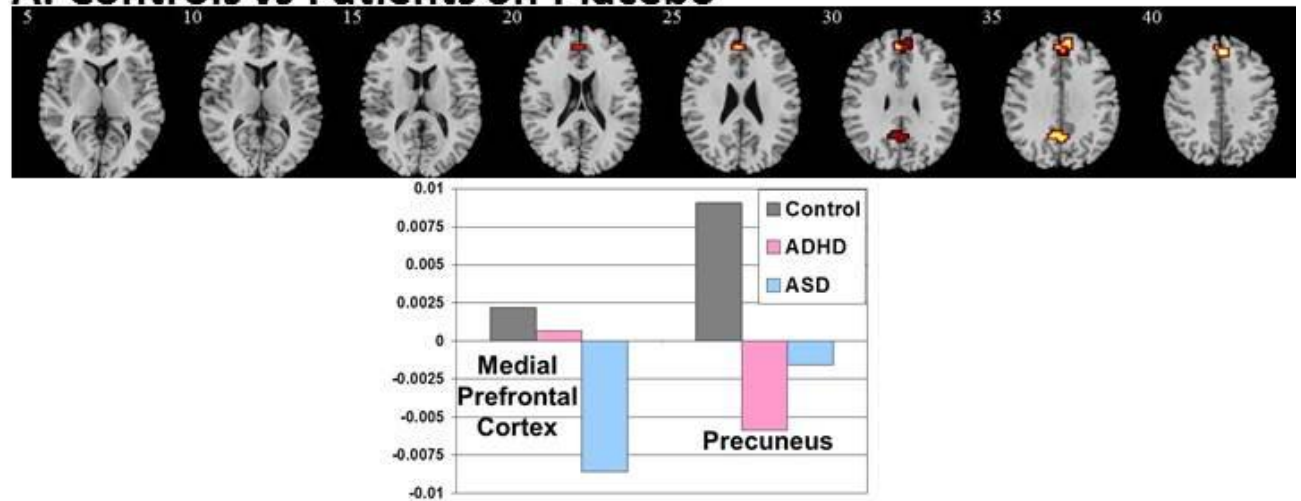
To assess the potential impact of IQ on case-control group differences, all analyses were repeated with IQ as covariate. All clusters remained at $p < 0.05$ for placebo and at $p < 0.02$ for Fluoxetine

Within-Patients group by medication interaction effects

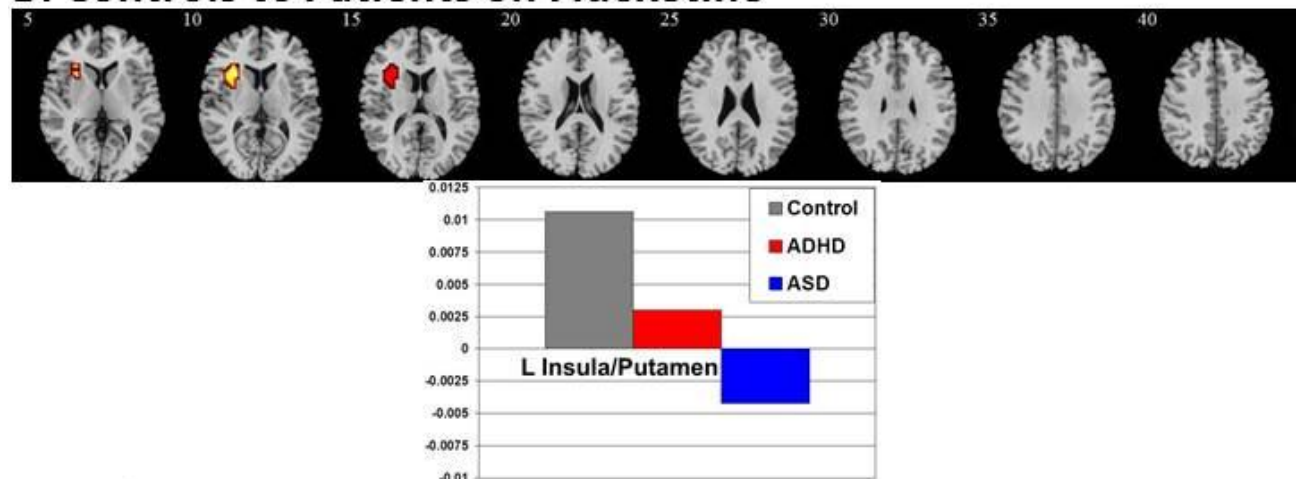
Repeated measures ANCOVA analysis showed a significant group by medication interaction effect in mPFC (41 voxels, peak Talairach coordinates (x;y;z): 0;63;15; BA10/9), due to Fluoxetine increasing activation in this area in the ASD group and decreasing it in the ADHD group (Figure 13.C). This remained significant at $p < 0.01$ when IQ was covaried for.

Between-Group Comparisons

A. Controls vs Patients on Placebo



B. Controls vs Patients on Fluoxetine



Within-Patient Comparisons

C. Group by Medication Interaction Effects

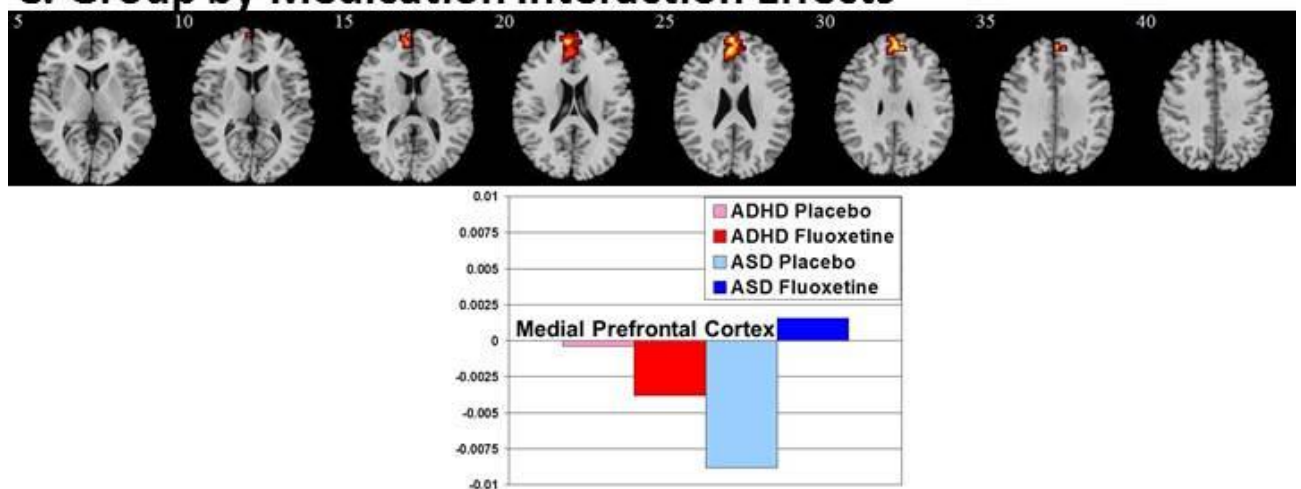


Figure 13.A. Reward Reversal Learning Between-Group and Within-Patient Comparisons: Axial sections showing the between-group ANCOVA findings between controls and patients under placebo. Shown underneath are the statistical measures of BOLD response for each of the 3 groups for each of the brain regions that showed a significant group effect. **B.** Axial sections for the between-group ANCOVA comparison between controls and patients under Fluoxetine. Shown underneath are the statistical measures of BOLD response for each of the 3 groups for each of the brain regions that showed a significant group effect. **C.** Axial sections showing within-patient group by medication interaction effects. Shown underneath are the statistical measures of BOLD response for each of the brain regions that showed a significant group by medication interaction effect within-patients. Talairach z coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 9. Brain activation differences during reward reversal learning between controls and patients on either placebo or Fluoxetine

Post-Hoc Group Differences	Brain regions of activation differences	Brodmann area (BA)	Talairach coordinates (x;y;z)	Voxels	Cluster p-value
PLACEBO					
ASD < C, ADHD	Left medial PFC	10/9	-4;52;20	23	0.016
ADHD, ASD < C	Precuneus/PCC	31/7	0;-52;26	11	0.016
FLUOXETINE					
ASD < C	Left Insula/Putamen	13	-33;19;4	23	0.007

7.4 – Discussion

This study shows that during the final stage of reward reversal, contrasted with probabilistic errors, ASD boys have disorder-specific underactivation in mPFC, a key region of reward-related decision making, relative to ADHD and control boys, as well as shared underactivation with ADHD boys, relative to controls, in precuneus, a key region of error processing. Fluoxetine had an inverse, disorder-specific effect in mPFC as it increased activation in ASD boys, leading to normalisation of their dysfunction relative to controls, but decreased activation in ADHD boys, concomitant with deteriorated task performance relative to controls. The findings suggest that Fluoxetine has disorder-dissociative, inverse modulatory effects on a key region of reward reversal learning, potentially reflecting differential baseline 5-HT levels in both disorders.

ASD boys compared to the other two groups showed disorder-specific underactivation in a key region of reward reversal (Finger et al., 2008, Remijnse et al., 2005, Mitchell et al., 2009a) and reward-related decision making (Euston et al., 2012) that is particularly sensitive to negative feedback, mediating shifting away from disadvantageous responses after negative feedback (Christakou et al., 2009a, Ghahremani et al., 2010). Dysfunction in mPFC in ASD may be related to evidence for abnormally increased grey matter in the mPFC in adolescent boys with ASD compared to controls (Bonilha et al., 2008), indicative of poor synaptic pruning, and of poor SERT binding in mPFC in ASD (Makkonen et al., 2008). Although ASD patients were not significantly impaired in the task they had numerically more perseverative errors with a medium effect size (0.5) which may have reached significance in a larger cohort. The disorder-specificity of the brain dysfunction to ASD was unexpected. However, the only previous fMRI study that used a very similar reward reversal task and contrast found normal mPFC activation in ADHD relative to controls (Finger et al., 2008). Together, the findings of these two studies suggest that mPFC underactivation may not be a neurofunctional feature of ADHD in the context of reward reversal learning. This contrasts with consistent evidence for lateral prefrontal underactivation in ADHD patients relative to controls during other cognitive control tasks that are mediated by more lateral prefrontal regions (Hart et

al., 2013, Smith et al., 2006, Rubia et al., 2010a, Rubia, 2011, Rubia et al., 2010b, Rubia et al., 2009d, Rubia et al., 2005b).

The shared dysfunction in precuneus is interesting as precuneus is closely interconnected with mPFC (Small et al., 2003) and plays a role in reversal learning (Dodds et al., 2008, Ghahremani et al., 2009), reward evaluation (McCoy and Platt, 2005, Liu et al., 2011) and visual-spatial attention to saliency, in particular error processing (Kravitz et al., 2011, Rubia et al., 2003, Rubia et al., 2007c, Small et al., 2003, Ridderinkhof et al., 2004). Findings of precuneus dysfunction in ADHD during reward reversal extends prior evidence for precuneus dysfunction in response to salient events such as errors and rewarded trials in other tasks (Rubia et al., 2009d, Rubia et al., 2005b, Rubia, 2011), presumably reflecting poor saliency and error processing. In ASD, the precuneus has been found to be underactivated during interference (Solomon et al., 2009) and motor inhibition (Kana et al., 2007). The association in ASD between precuneus dysfunction and perseverative errors supports the notion that this dysfunction may reflect poor error processing, even if these did not reach significance relative to controls.

The most intriguing finding is the inverse effect of Fluoxetine on mPFC activation in the two disorders, upregulating and normalising it in ASD but decreasing it in ADHD. This inverse effect could potentially reflect disorder differences in baseline 5-HT levels. Approximately 30% of individuals with ASD have hyperserotonemia (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007). There is evidence for reduced binding to SERT in the mPFC of individuals with ASD (Makkonen et al., 2008, Nakamura et al., 2010) as well as reduced 5-HT_{2A} receptor binding (Murphy et al., 2006) and altered 5-HT synthesis (Chugani et al., 1999, Chugani et al., 1997). This suggests that hyperserotonemia may be an adaptation to counteract poor 5-HT receptor binding and abnormal 5-HT synthesis. The increase in 5-HT with Fluoxetine may have increased ligand-receptor binding sufficiently to enhance activation in areas where 5-HT receptor density is particularly low. In addition, Fluoxetine may have amended an abnormal “balance” of 5-HT, therefore improving the homeostatic role of this key neurotransmitter and potentially leading to an increase in mPFC activation in ASD (Murano et al., 2011, Di Pietro and Seamans, 2011). Furthermore, each brain region has a distinct serotonergic profile, with limbic

and more medial structures receiving dense serotonergic innervation (Varnäs et al., 2004, Jacobs and Azmitia, 1992). This therefore makes regions such as the mPFC highly susceptible to serotonergic manipulation, particularly in a patient group which have shown structural (Bonilha et al., 2008) and biochemical (Makkonen et al., 2008, Nakamura et al., 2010, Murphy et al., 2006) abnormalities in this region. It is also plausible that an increase in 5-HT may be modulating primary 5-HT abnormalities in transporter function (Makkonen et al., 2008, Nakamura et al., 2010) or 5-HT_{2A} receptor binding (Murphy et al., 2006), which have been reported to be impaired in the mPFC of ASD individuals (Makkonen et al., 2008, Nakamura et al., 2010, Murphy et al., 2006), and may have led to the increased activation in mPFC observed in the ASD group. Our finding of an upregulation and normalisation in the mPFC of adolescents with ASD under Fluoxetine extends prior evidence that SSRIs increase metabolic and neurofunctional activity in prefrontal areas in adults with ASD (Buchsbaum et al., 2001, Dichter et al., 2010).

Fluoxetine also decreased insula activation in ASD relative to controls. The insula forms part of a mPFC-limbic network for reward-related decision making, and like mPFC, is particularly sensitive to negative feedback and mediates shifting away from disadvantageous choices (Christakou et al., 2009a). The normalisation of mPFC with Fluoxetine may have resulted in the impairment of a limbic part of the reversal network, suggesting that brain function was not entirely normalised.

The inverse reduction of activation in mPFC in ADHD with Fluoxetine was unexpected. However, ADHD boys, unlike ASD boys, showed no underactivation in this region and hence the 5-HT modulation may have interfered with normal prefrontal activation. This is further supported by the finding of performance impairment with 5-HT in ADHD. While ADHD patients have shown lateral prefronto-striatal underactivation during switching tasks (Smith et al., 2006, Rubia et al., 2010b, Rubia et al., 2010a, Hart et al., 2013), the only previous fMRI study on a similar contrast in a reward reversal task found normal mPFC activation in ADHD relative to controls (Finger et al., 2008). Hence, reward reversal learning tasks may not elicit underactivation in key areas of reversal processes and consequently not tap into the dysfunctional brain mechanisms of ADHD. Furthermore, although there is evidence of serotonergic dysfunction in ADHD, the direction and implications of

these abnormalities are still unclear (Oades, 2007). In ASD, however, there is a wealth of research supporting the presence of genetic and biochemical serotonergic abnormalities (Zafeiriou et al., 2009, Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007, Chugani et al., 1999, Chugani et al., 1997, Makkonen et al., 2008, Nakamura et al., 2010, Murphy et al., 2006, Buchsbaum et al., 2001, Dichter et al., 2010) which may have accounted for the positive upregulation effect of Fluoxetine on ASD mPFC activation and its negative downregulating effect on mPFC activation in ADHD. Interestingly, a decrease in 5-HT with ATD has been shown to lead to increased activation in the mPFC in healthy individuals during a task of reward reversal learning (Evers et al., 2005). Therefore, it appears as if ADHD children are exhibiting a similar pattern of serotonergic neurofunctional modulation to healthy controls in a brain region which is not impaired in the disorder. Consequently, Fluoxetine may interfere with this normal brain function in ADHD in this task context, leading to decreased activation.

The strengths of this study are the carefully selected, non-comorbid patient groups and the medication-naivety of the ASD group. A limitation is the lower IQ in the ADHD group. However covariance analysis showed that this did not affect the main findings.

To summarise, we found disorder-specific underactivation in ASD boys in mPFC, a key region of reversal learning, as well as disorder-dissociated inverse effects of Fluoxetine on this region, with upregulated and normalised dysfunction in ASD but downregulated activation in ADHD, concomitant with worsening their task performance. The findings may indicate dissociated underlying 5-HT abnormalities in the two disorders.

Chapter 8 – General Discussion

8.1 – Summary

ADHD and ASD are two neurodevelopmental disorders which are frequently co-morbid (Rommelse et al., 2011, van der Meer et al., 2012) and share executive function impairments (Willcutt et al., 2005, Corbett et al., 2009). In addition, there is evidence of serotonergic dysfunction, and a positive effect of the SSRI Fluoxetine, in both ADHD (Oades, 2007, Barrickman et al., 1991, Quintana et al., 2007) and ASD (Zafeiriou et al., 2009, West et al., 2009). However, the shared and disorder-specific neural underpinnings of the cognitive impairments in these disorders, as well as the modulating effect of Fluoxetine on these potential neurofunctional abnormalities, has yet to be investigated. This thesis has, for the first time, 1) used fMRI to compare boys with ADHD and boys with ASD during tasks of working memory, motor response inhibition and cognitive flexibility and 2) investigated the shared and disorder-specific effects of an acute clinical dose of Fluoxetine on these neural substrates in a double-blind, placebo controlled, randomised design. The results show both disorder-specific and shared dysfunctions in boys with ADHD and boys with ASD under placebo, compared to controls. Most importantly, an acute dose of Fluoxetine appears to have mainly inverse effects on the regulation of prefrontal brain activation in the two disorders, although there is also evidence for shared effects.

During WM, behavioural case-control comparisons showed no group differences under placebo, but the within-group analysis showed a trend for increased accuracy in patients under Fluoxetine, relative to placebo. fMRI data showed that under placebo, both ADHD and ASD boys exhibited shared reduced activation in right DLPFC compared to controls, with a trend for the ASD group to be more impaired than the ADHD group. ASD boys exhibited disorder-specific increased deactivation of PCC compared to control and ADHD boys. Under Fluoxetine, case-control comparisons showed that the DLPFC underactivation was normalised in both disorders relative to controls, but only significantly so in the ASD group. The within-patient analysis showed that Fluoxetine relative to placebo had an inverse effect in both disorders on the task negative PCC deactivation, as it increased deactivation in

the ADHD group, making it significantly different from controls, and attenuated it in the ASD group, who were still significantly different from controls in this activation cluster, but no longer significantly different from ADHD. Therefore, during WM Fluoxetine had disorder-dissociated effects in the regulation of brain function as it significantly upregulated and normalised task-positive DLPFC activation in the ASD group, whereas it increased task negative deactivation of a DMN area in the ADHD group. Both of these dissociated brain modulation effects appear to be associated with better performance as both patient groups were more accurate, at a trend-level, relative to placebo.

During motor response inhibition, performance data showed no group differences for inhibition measures and no effect of Fluoxetine on these measures. However, boys with ADHD made more omission errors compared to controls and ASD boys under both placebo and Fluoxetine. fMRI data showed that under placebo, boys with ADHD exhibited disorder-specific underactivation of left VLPFC/basal ganglia compared to controls and ASD boys, while ASD boys exhibited disorder-specific increased bilateral IFC activation compared to controls and ADHD boys. Shared underactivation of left inferior parietal lobe was observed in both disorders compared to controls. Fluoxetine relative to placebo modified brain activation in an inverse manner in the two disorders, leading to significant normalisation of all frontal abnormalities in both disorders relative to controls. This was confirmed by the within-patient analysis which showed that Fluoxetine relative to placebo increased left VLPFC activation in ADHD, while decreasing this activation in ASD, and decreased the right IFC activation in ASD, while increasing it in ADHD. Fluoxetine relative to placebo also had an inverse effect in left inferior parietal activation as it significantly increased activation in the ASD group, leading to significant normalisation, but decreased activation in this area in the ADHD group. An inverse effect was also noted in pre-SMA/mPFC extending into left middle/superior frontal cortex as Fluoxetine compared to placebo increased activation in these regions in the ASD group, which correlated with shorter SSRTs, while decreasing activation in these regions in the ADHD group. The findings show that during motor response inhibition, Fluoxetine normalises frontal lobe dysfunctions in both disorders via inverse effects, downregulating abnormally high frontal activation in ASD and upregulating abnormally low frontal activation in ADHD.

During reward reversal learning, performance data showed that under placebo, the patient groups did not differ from controls, but under Fluoxetine boys with ADHD made significantly more perseverative errors than controls. Case-control comparisons showed that under placebo, ASD boys had disorder-specific underactivation of mPFC compared to controls and ADHD, and that both patient groups significantly underactivated precuneus compared to controls. Under Fluoxetine the mPFC deficit in ASD compared to controls and ADHD was significantly normalised. This was confirmed by within-patient analyses which showed that Fluoxetine relative to placebo increased activation in mPFC in ASD patients. However, Fluoxetine had the inverse effect in ADHD as it reduced activation in this region relative to placebo. Precuneus activation was increased in both disorders under Fluoxetine relative to placebo. However it did not significantly normalise the deficit in either disorder relative to controls. A further disorder-specific effect of Fluoxetine was observed in the ASD group, under Fluoxetine, but not under placebo, the insula activation was reduced in ASD relative to controls. The findings show disorder-specific underactivation in ASD boys in mPFC, as well as disorder-dissociated inverse effects of Fluoxetine on this region, which upregulated and normalised dysfunction in ASD but downregulated activation in ADHD, concomitant with worsening their task performance.

The findings of each of these studies will be discussed in detail below in order to assess the shared and disorder-specific dysfunctions in boys with ADHD and ASD, and the shared and disorder-specific modulating effect of Fluoxetine on brain activation in these two overlapping disorders.

8.2 – Disorder-Specific Dysfunction

This section will focus on the disorder-specific findings for each patient group under placebo.

In the ADHD group, the only disorder-specific brain dysfunction across all tasks relative to ASD was observed in a left hemispheric, ventrolateral fronto-striatal

activation cluster during motor response inhibition, and this neurofunctional abnormality was observed alongside poor task performance, in the form of increased omission errors. This finding of underactivation in VLPFC is in line with previous findings, as it has been consistently reported that children with ADHD have reduced ventrolateral frontal and striatal activation during tasks of motor response inhibition (Rubia et al., 1999, Rubia et al., 2010a, Tamm et al., 2004, Rubia et al., 2011a, Durston et al., 2003, Durston et al., 2006, Booth et al., 2005, Smith et al., 2006, Epstein et al., 2007), and this neural dysfunction has been confirmed by a meta-analysis of all whole brain fMRI studies (Hart et al., 2013). However, the location of the underactivation observed in this study was more ventral than the typically reported IFC location. Also, although we hypothesised right IFC underactivation in the ADHD group there have been previous findings of left IFC underactivation in children with ADHD during motor response inhibition, and there is evidence that left, as well as right, IFC is involved in motor response inhibition (Rubia et al., 2001a, Tamm et al., 2002, Swick et al., 2008). Furthermore, progressively increased left VLPFC and striatal activation during motor response inhibition has been reported to correlate positively with age (Tamm et al., 2002, Rubia et al., 2007c). Therefore, underactivation in this region in the ADHD group relative to their age-matched peers is suggestive of an immature pattern of brain activation. Consequently, this finding not only replicated the consistent evidence for fronto-striatal underactivation in ADHD during motor response inhibition (Cubillo et al., 2012), but showed for the first time that this abnormality is disorder-specific when compared to ASD.

Conversely, in ASD, increased activation was observed in bilateral IFC during motor response inhibition, compared to controls and ADHD boys. Increased left IFC activation has been previously reported in adults with ASD during a Go/No-Go task (Schmitz et al., 2006). However, this is the first time this abnormality has been reported in children. It is also the first time this overactivation has also been observed in the right IFC. This increased bilateral IFC activation may be due to children with ASD having to exert more effort in these key areas of inhibition (Rubia et al., 2001a, Rubia et al., 2003, Rubia et al., 2006, Rubia et al., 2007c) to successfully inhibit their motor response, as they are prone to becoming locked in to the repetitive motor action of pressing the button.

These disorder-specific abnormalities in the neural substrates of inhibition may play a role in the different inhibition associated behaviours observed in the two disorders. Impaired inhibition in ADHD is exhibited by impulsive behaviour such as blurting out answers and interrupting conversations (American et al., 1994). However, in ASD impaired inhibition is thought to be associated with the inability to inhibit particular actions, leading to repetitive behaviours (American et al., 1994). Therefore, decreased activation in ventrolateral fronto-striatal areas in ADHD may lead to reduced ability to inhibit responses, resulting in the impulsive behaviours that are characteristic of this disorder. Conversely, increased IFC activation in ASD may have a different effect on inhibition, resulting in different behavioural manifestations such as repetitive and stereotyped actions. However, as this thesis found no performance differences in SSRT, another potential explanation for these different neurofunctional abnormalities is that unlike the children with ASD, the children with ADHD were not at risk of becoming locked into the repetitive action of button pressing. Therefore, normal right IFC activation, potentially compensating for VLPFC underactivation, may have been sufficient for normal task performance, with regards to inhibitory measures, in the ADHD group. However, due to their propensity for repetitive behaviours, boys in the ASD group may have had to exert more effort in these key regions of inhibition in order to successfully inhibit their motor response.

In addition, during the Stop Signal task left inferior parietal cortex was underactivated in ASD boys compared to controls. Therefore, one can postulate that in the ASD group, during inhibition, the increased activation in IFC may also have been a compensation for reduced activation in left inferior parietal lobe. There is evidence that inferior parietal lobe is involved in attention to salient stimuli and this is integral to successful Stop Signal task performance (Rubia et al., 2001a, Simmonds et al., 2008). Consequently, in the ASD group more neurofunctional activity may have been required in IFC in order to compensate for reduced activation in attention areas.

Although there is neuropsychological evidence for poor motor response inhibition in children with ADHD (Willcutt et al., 2005) and children with ASD (Hill, 2004, O'Hearn et al., 2008, Sanders et al., 2008), in this study no performance differences were observed for the inhibitory measure of SSRT. This may be due to the size of the sample in this study as although the number of subjects in each group is

adequate for fMRI, it is relatively small for a neuropsychological study (Thirion et al., 2007). Furthermore, practice effects in the patient groups may have prevented significant between-group differences in inhibitory measures as controls were only scanned once, but patients twice. This may also account for the lack of significant between-group performance differences during WM.

During WM, disorder-specific increased deactivation of the PCC was reported in the ASD group relative to controls and ADHD. It is known that PCC is part of the DMN and that deactivation of these task-negative DMN regions is associated with better task performance and less mind wandering, in particular during attention-demanding tasks, (Fox et al., 2005, Raichle and Snyder, 2007, Northoff et al., 2010). Therefore, the increased deactivation of PCC in the ASD group may be compensating for underactivation in the key task positive WM region of DLPFC, and the trend-wise more severe deficit in this area in ASD compared to ADHD may further explain the disorder-specificity of this finding.

During reward reversal learning, the only disorder-specific abnormality reported was underactivation of mPFC in the ASD group as compared to controls and ADHD boys. There is consistent evidence to support the role of mPFC in reward reversal learning (Finger et al., 2008, Remijnse et al., 2005, Mitchell et al., 2009a), reward related decision making (Euston et al., 2012) and shifting away from poor choices after negative feedback (Christakou et al., 2009a, Ghahremani et al., 2010). Decreased activation in ACC, an anatomically and functionally related area to mPFC (Ridderinkhof et al., 2004), has been reported in adults with ASD during a switch task and this underactivation was correlated with stereotyped behaviours (Shafritz et al., 2008). Atypical activation of mPFC has also been observed in individuals with ASD during an executive function task focusing on stimulus-orientated and stimulus-independent thought (Gilbert et al., 2008). Interestingly, a meta-analysis of executive functions in ASD found decreased activation of dorsal ACC compared to controls (Di Martino et al., 2009). Structural studies have found increased grey matter in the mPFC of adolescents with ASD (Bonilha et al., 2008). These findings, along with our own, tentatively suggest that mPFC abnormality may be a defining neurofunctional deficit of ASD during tasks of executive functions, particularly those targeted at cognitive

flexibility. Furthermore, our findings extend this evidence by showing that mPFC underactivation may be a disorder-specific feature of ASD relative to ADHD.

So to summarise, there appeared to be disorder-specific, and task-specific, dysfunctions present between boys with ADHD and boys with ASD. Ventrolateral fronto-striatal abnormalities appeared to be specific for boys with ADHD during motor response inhibition, whereas IFC overactivation appeared to be specific for boys with ASD during the same task. Increased PCC deactivation, presumably compensatory for the more severe DLPFC underactivation, was disorder-specific for ASD boys during WM. mPFC underactivation during reward reversal learning was an abnormality which was specific to ASD, compared to controls and ADHD, and structural (Bonilha et al., 2008) and functional studies (Shafritz et al., 2008, Gilbert et al., 2008, Di Martino et al., 2009) are beginning to show that mPFC/ACC may be a key area of structural and functional abnormality in ASD. The disorder-specificity of the findings from this thesis are highly intriguing and potentially suggest that (ventrolateral) fronto-striatal underactivation in ADHD during tasks motor response inhibition, and mPFC underactivation in ASD during reward reversal learning, could potentially be disorder-specific neurofunctional biomarkers of the two disorders and could therefore be used to differentiate between ADHD and ASD. However, further research is needed to confirm or refute these novel findings.

VLPFC was negatively correlated with omission errors in the ADHD group, suggesting that this deficit was associated with poor attention to the Stop Signal task. This ventrolateral fronto-striatal underactivation was specific to ADHD and this may be due to the inhibition deficits that are present in this disorder (Willcutt et al., 2005, Lijffijt et al., 2005, Alderson et al., 2007, Adams et al., 2008). Despite the lack of performance differences in inhibitory measures in this study, it is known that impulsivity and poor inhibition are key diagnostic features of ADHD (American et al., 1994), and there is neuropsychological evidence that ADHD children are more impaired in motor response inhibition than both controls and ASD children (Happé et al., 2006, Sinzig et al., 2008). In this study, patients performed the task twice while controls did so only once and this may have diminished performance differences. Furthermore, ventrolateral fronto-striatal regions are involved in motor response inhibition in healthy individuals (Rubia et al., 2001a, Rubia et al., 2003, Rubia et al.,

2007c, Rubia et al., 2006, Chambers et al., 2009). Therefore, it is reasonable to suggest that in a patient group which is characterised by impaired inhibition, disorder-specific underactivation, compared to controls and ASD, would be observed in inhibition areas during a task of motor response inhibition.

Disorder-specific underactivation in mPFC in boys with ASD, compared to controls and ADHD, is also in line with the key cognitive and behavioural impairments reported in this disorder. Stereotyped and repetitive behaviours are part of the ASD diagnostic triad (American et al., 1994)(APA 1994) and despite the lack of performance deficits in ASD boys in this thesis, there is evidence for poor cognitive flexibility in this disorder (Geurts et al., 2004, Ozonoff et al., 2004, Verte et al., 2005, Sanders et al., 2008) with some studies finding that this impairment is specific to ASD compared to both controls and ADHD (Ozonoff and Jensen, 1999, Geurts et al., 2004). Moreover, mPFC is involved in reversal learning and decision making in healthy individuals (Remijnse et al., 2005, Finger et al., 2008, Mitchell et al., 2009a, Euston et al., 2012). Consequently, disorder-specific reduced activation in this key area of cognitive flexibility in ASD, a disorder that is significantly impaired in this executive function, albeit not in this thesis, could reflect more severe abnormalities in neural substrates underlying this function.

8.3 – Shared Dysfunction

This section will focus on the shared abnormalities between boys with ADHD and boys with ASD under placebo.

During WM, both boys with ADHD and boys with ASD showed decreased activation in right DLPFC compared to controls, with ASD boys being more impaired than ADHD boys, at a trend-level. DLPFC is a key area for the storage and manipulation of information during WM (Wager and Smith, 2003) and there is prior evidence for decreased activation in this area in male children (Cubillo et al., 2013) and adults (Valera et al., 2010) with ADHD, and in adults with ASD during similar WM tasks (Luna et al., 2002, Koshino et al., 2005). Furthermore, it has been reported that during a parametric sustained attention task, boys with ADHD and boys with

ASD show shared decreased activation in left DLPFC (Christakou et al., 2013). Therefore, the findings of the current study support the presence of DLPFC underactivation in children with ADHD, and find for the first time that right DLPFC is underactivated in children with ASD, during WM compared to controls.

In addition, these findings, alongside those of Christakou et al, 2013, suggest that DLPFC underactivation may be shared by both children with ADHD and children with ASD during tasks of attention and WM. Right DLPFC underactivation was a key finding in a meta-analysis of whole brain imaging studies of attention in ADHD (Hart et al., 2013), and it is known that WM paradigms tap into attention functions as attention needs to be sustained in order to perform the task. There is behavioural and neuropsychological evidence for impaired attention in both ADHD (American et al., 1994, Willcutt et al., 2005, Rubia et al., 2007a) and ASD (Sturm et al., 2004, Corbett and Constantine, 2006, Corbett et al., 2009, Simonoff et al., 2008). Therefore, deficits in DLPFC, a key area of attention, may explain the shared difficulties in sustained attention that are commonly observed in both ADHD and ASD.

During motor response inhibition, reduced activation was observed in left inferior parietal lobe in both boys with ADHD and boys with ASD, relative to controls. Although the inferior parietal lobe is considered an area of visual-spatial attention (Bisley and Goldberg, 2010), this function is essential for a visual Stop task, and inferior parietal lobe has therefore consistently been found to be relevant for motor response inhibition in a recent meta-analysis of Go/No-Go tasks (Criaud and Boulinguez, 2012) . The only previous fMRI study to directly compare boys with ADHD and boys with ASD is from our group, and found shared decreased activation in right DLPFC and left superior parietal lobe during a parametric sustained attention task (Christakou et al., 2013). Interestingly, a comparative sMRI study of children with ADHD and children with ASD found shared reduced grey matter in left inferior parietal lobe compared to controls, although this did not survive testing for multiple comparisons (Brieber et al., 2007). Furthermore, a recent study of cerebral blood flow in adults with ASD found that an increase in ADHD traits was correlated with increased blood flow in inferior parietal lobe (Manouilenko et al., 2013). The inferior parietal lobe is involved in orientation of attention (Bisley and Goldberg, 2010) and as previously discussed, both children with ADHD (American et al., 1994, Willcutt et

al., 2005, Rubia, 2007) and children with ASD (Sturm et al., 2004, Corbett and Constantine, 2006, Corbett et al., 2009, Simonoff et al., 2008) have behavioural and cognitive impairments in attention. Consequently, decreased activation in this key region of visuo-spatial attention in both ADHD and ASD may be due to both groups struggling with the attentional demands of the task and suggests that attention difficulties in both disorders may be mediated by common neural substrates.

During reward reversal learning reduced activation was observed in precuneus in both ADHD and ASD boys compared to controls. There is evidence for the role of precuneus in reversal learning (Dodds et al., 2008, Ghahremani et al., 2010) and reward evaluation (McCoy and Platt, 2005, Liu et al., 2011) as well as attentional orientation and allocation (Kravitz et al., 2011). Decreased precuneus activation has been observed in boys with ADHD during error processing (Rubia et al., 2005b, Rubia et al., 2010a)(Rubia et al 2005, 2009, 2010), as well as attention allocation to rare stimuli, (Rubia et al., 2007b, Rubia et al., 2009c, Rubia et al., 2009b), and in individuals with ASD during interference and motor response inhibition (Solomon et al., 2009, Kana et al., 2007). However, it was observed that precuneus activation correlated positively with perservative errors in the ASD group. This may be because an increase in activation in this area would increase attention, potentially causing the ASD boys to hyper-focus on the stimuli, and this, in addition to reduced activation in mPFC, a key area for reversal learning, may lead to more repetitive and perservative responses. Moreover, there is evidence that attentional over-selectivity is linked to repetitive behaviours in ASD (Liss et al., 2006). Therefore, although both ADHD and ASD boys exhibit decreased activation in precuneus, this may be positive for the ASD group, in the context of mPFC underactivation, due to their propensity to hyper-focus (Liss et al., 2006), and negative in the ADHD due to their poor ability to sustain attention (Willcutt et al., 2005).

The findings from this thesis, as well the limited neuroimaging research focused on direct comparisons between ADHD and ASD, suggest that dorsolateral frontal and inferior parietal underactivation are shared between the disorders. A shared neurofunctional activation deficit in areas that are crucial for attention could possibly explain why both disorders have deficits in attention functions, both

behaviourally as well as in cognitive task performance (American et al., 1994, Willcutt et al., 2005, Rubia et al., 2007a, Sturm et al., 2004, Corbett and Constantine, 2006, Corbett et al., 2009, Simonoff et al., 2008). While the patients of this study were non-comorbid, the shared underactivation in these key areas of attention could possibly underlie the comorbidity that some children have with both disorders. Future research should focus on the inferior parietal lobe as a potential key area for comorbidity between ADHD and ASD as both functional (Christakou et al., 2013) structural (Brieber et al., 2007) and metabolic (Manouilenko et al., 2013) abnormalities appear to be shared between these two disorder in this key region of attention.

8.4 – Disorder Dissociated Fluoxetine Effects

This section will focus on the disorder-dissociated effects of Fluoxetine on brain activation in boys with ADHD and boys with ASD.

Interestingly, Fluoxetine consistently had inverse, disorder-dissociated effects in mostly prefrontal brain regions where disorder-specific deficits were observed under placebo. Thus, within patients, Fluoxetine relative to placebo increased activation in left ventrolateral fronto-striatal regions in ADHD during motor response inhibition, leading to significant normalisation of this deficit in ADHD relative to controls, while it enhanced activation in this region in ASD. The inverse effect was observed for the enhanced IFC activation in ASD relative to ADHD and controls, which was downregulated in ASD but upregulated in ADHD.

There is evidence for serotonergic dysfunction in ADHD (Oades, 2007) and although the direction of this dysfunction is unclear, there is evidence for decreased platelet 5-HT levels in boys with ADHD (Spivak et al., 1999). Furthermore, it has been observed that ATD, which diminishes 5-HT levels in the brain, leads to poorer performance on a Go/No-Go task (Zepf et al., 2008a), and increased impulsive aggression, in children with ADHD (Zepf et al., 2009, Zepf et al., 2008c, Stadler et al., 2007). It has also been consistently reported that lower levels of 5-HT are associated with impulsivity in both animals and healthy individuals (Robbins et al.,

2010). Moreover, fMRI studies on healthy adults during a Go/No-Go task have shown that ATD leads to decreased activation in VLPFC (Rubia et al., 2005a), and that administration of Citalopram leads to increased VLPFC activation (Del-Ben et al., 2005). Therefore, one could postulate that the ADHD cohort in this study may have had low baseline levels of 5-HT, which may have led to underactivation in ventrolateral fronto-striatal areas under placebo. This could explain why an increase in 5-HT, induced by Fluoxetine, increased activation in this area leading to normalisation of the underactivation relative to controls. This is of particular interest as it suggests that 5-HT may play a role in the fronto-striatal underactivation that has consistently been reported in ADHD during motor response inhibition. As mentioned in the introduction, due to the low levels of dopamine in fronto-striatal regions in ADHD patients (Volkow et al., 2009, del Campo et al., 2011), fronto-striatal underactivation in ADHD during inhibition (Cubillo et al., 2012) and the positive effect of MPH on behaviour (Greenhill et al., 2001), performance (Gnagy et al., 2001) and fronto-striatal regions in the disorder (Rubia et al., 2009b, Rubia et al., 2011b, Rubia et al., 2011c), research in ADHD has focused on dopamine, at the expense of other key neurotransmitters such as 5-HT.

5-HT is one of the most wide reaching neurotransmitters in the brain and, like dopamine, is found in both frontal and striatal regions (Feldman et al., 1997, Tork, 1990). Akin to dopamine, there is evidence that 5-HT plays an integral role in VLPFC activation during motor response inhibition, with an increase/decrease in 5-HT leading to an increase/decrease in activation, respectively (Rubia et al., 2005a, Del-Ben et al., 2005). It has also been shown that Fluoxetine alone (Barrickman et al., 1991, Quintana et al., 2007), or in conjunction with MPH (Gammon and Brown, 1993) can improve hyperactivity and impulsivity in children with ADHD. Therefore, much like dopamine, there is behavioural and neurofunctional evidence that 5-HT may play a role in ADHD. This thesis provides evidence that 5-HT appears to be involved in ventrolateral fronto-striatal deficits in ADHD, because Fluoxetine can upregulate and normalise these deficits. This is the first time that this has been reported and shows that 5-HT may be as equally involved as dopamine in the key fronto-striatal pathophysiology of ADHD as dopamine. Furthermore, it is known that serotonergic neurons innervate the ventral tegmental area and modulate both phasic and tonic dopamine release (Feldman et al., 1997, Tork, 1990). Therefore, the

interaction between dopamine-serotonin, as well as the absolute levels of these two neurotransmitters, may also play a role in the fronto-striatal deficits observed in ADHD

This normalising effect of Fluoxetine appears to be region-specific as although Fluoxetine in ADHD patients increased activation in DLPFC, and increased deactivation of PCC, during WM, and increased activation of precuneus during reward reversal learning, rigorous normalisation testing showed that these positive neurofunctional modulations were not significant. The region-specificity of the normalisation effects of Fluoxetine, on VLPFC but not DLPFC or medial parietal regions, may be due to the dense serotonergic innervation in VLPFC regions (Roberts, 2011), resulting in high levels of sensitivity to 5-HT manipulation in these areas, particularly during motor response inhibition (Rubia et al., 2005a, Del-Ben et al., 2005). Moreover, there is more evidence for the role of 5-HT in impulsivity and inhibition compared to WM (Anderson et al 2008, Silber et al 2009), which is thought to be mediated more by dopaminergic and noradrenergic systems (Cools and D'Esposito, 2011) . It has been observed that Atomoxetine is able to significantly normalise right DLPFC underactivation in boys with ADHD during the same N-Back task (Cubillo et al., 2013). Therefore, it appears as if Fluoxetine not only has disorder-specific effects in ADHD on VLPFC, but also region-specific effects as it normalised deficits in serotonergically innervated VLPFC-striatal inhibition networks in ADHD, but did not do so in DLPFC mediated WM networks, and this may potentially be because noradrenergic/dopaminergic abnormalities play a larger role in these deficits.

In the ASD group, however, the opposite effect was observed in this region as the within patient interaction analysis showed that Fluoxetine decreased activation in VLPFC/basal ganglia compared to placebo. Fluoxetine also decreased the IFC overactivation that was present in the ASD group under placebo, relative to controls and ADHD, leading to significant normalisation of this deficit. The opposite effect was observed in right IFC in the ADHD group in the within patient interaction analysis as Fluoxetine increased activation in this area relative to placebo. The opposite effect of Fluoxetine in these lateral prefrontal brain regions may be due to the differential serotonergic abnormalities that have been reported in these two

neurodevelopmental disorders. As previously mentioned, there is evidence for low 5-HT levels in individuals with ADHD (Spivak et al., 1999) and increased impulsivity in children with ADHD after ATD (Stadler et al., 2007, Zepf et al., 2008a, Zepf et al., 2008c). However, the converse has been reported in ASD as there is consistent evidence for hyperserotonemia in one third of individuals with ASD (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007). Therefore, Fluoxetine may have increased the low baseline of 5-HT in children with ADHD to normal levels, leading to normal activation in ventrolateral fronto-striatal areas. Whereas in children with ASD, the increase in 5-HT in an already hyperserotonemic system may have activated a negative feedback mechanism via activation of 5-HT_{1A} autoreceptors (Di Matteo et al., 2008), leading to a decrease in 5-HT and resulting in a reduction of lateral prefrontal activation. Therefore, it appears as if Fluoxetine increased activation in ventrolateral prefrontal and striatal areas of underactivation in ADHD, whereas it decreased activation in these same areas in ASD.

Interestingly, in other frontal regions, Fluoxetine, relative to placebo, had inverse upregulation-downregulation effects. Fluoxetine relative to placebo increased activation in pre-SMA/mPFC extending into left superior/middle frontal cortex in ASD, while decreasing activation in this area in ADHD. This increased pre-SMA/mPFC activation in the ASD group was correlated with better SSRTs which is in line with the key role of pre-SMA in motor response inhibition (Simmonds et al., 2008). This increased pre-SMA activation may have been a compensation for the reduction in IFC activation, another key area of inhibition. Alternatively, the increase in pre-SMA activation under Fluoxetine may have reduced the need for IFC overactivation, and this is in line with the association between increased pre-SMA activation and shorter SSRTs.

During another task, the reward reversal learning task, and in other frontal brain regions, different upregulation/downregulation effects were observed with Fluoxetine. Disorder-specific mPFC underactivation in ASD relative to placebo was normalised under Fluoxetine. Whereas in ADHD, under Fluoxetine, relative to placebo, mPFC activation was downregulated and this presumably led to the increased number of perseverative errors made by the ADHD group under Fluoxetine, relative to controls. As previously stated, there is a growing body of research to

suggest that mPFC underactivation during executive function may be a key impairment in ASD (Shafritz et al., 2008, Di Martino et al., 2009, Gilbert et al., 2008), and when taking into account the current findings, may in fact be disorder-specific to ASD when compared to ADHD. Interestingly, compared to other brain regions, there is quite a large amount of evidence for serotonergic abnormality in the mPFC of individuals with ASD. Decreased 5-HT transporter binding in mPFC has been reported in both adolescents (Makkonen et al., 2008) and adults (Nakamura et al., 2010) with ASD, as has decreased binding to 5-HT_{2A} receptors in mPFC in adults with ASD (Murphy et al., 2006). Impaired metabolism in the right mPFC of ASD individuals with the s/s genotype of 5-HTTLPR has also been observed (Endo et al., 2010) and metabolic activity in mPFC has been associated with better response to Fluoxetine (Buchsbaum et al., 2001). Furthermore, ATD in ASD adults during processing of a happy face led to decreased activation in dmPFC (Daly et al., 2012). This suggests that hyperserotonemia may be an adaptation to counteract serotonergic abnormalities in mPFC, which may possibly be the result of genetic polymorphisms. The increase in 5-HT induced by Fluoxetine may have increased ligand-receptor binding sufficiently to enhance activation in areas where serotonergic functioning is particularly low, such as mPFC.

The inverse effect of Fluoxetine in reducing mPFC activation in ADHD boys during reward reversal learning may be due to the fact that ADHD boys showed no underactivation in this region under placebo and hence Fluoxetine may have interfered with normal prefrontal activation. Furthermore, although there is evidence of serotonergic dysfunction in ADHD, the direction and implications of these abnormalities are still unclear (Oades, 2007). Interestingly, a decrease in 5-HT with ATD has been shown to lead to increased activation in the mPFC in healthy individuals during a task of reward reversal learning (Evers et al., 2005). Therefore, it appears as if ADHD children are exhibiting a similar pattern of serotonergic neurofunctional modulation to healthy controls in a brain region which is not impaired in the task. Consequently, Fluoxetine may interfere with this normal brain function in ADHD in this task, leading to decreased activation and poor task performance.

Fluoxetine also had an inverse effect on the activation of posterior medial brain regions that are involved in the DMN, namely PCC, during WM. Fluoxetine,

relative to placebo, attenuated the disorder-specific enhanced PCC deactivation in the ASD group, whereas it increased PCC deactivation in the ADHD group. The increased deactivation of PCC in ADHD under Fluoxetine may be due to the effect of an increase in 5-HT on the 5-HT_{2C} receptors in this area which would lead to a decrease in dopamine (Di Matteo et al., 2008). There is consistent evidence for decreased dopamine levels in individuals with ADHD in the basal ganglia and cingulate gyrus (Volkow et al., 2009, del Campo et al., 2011) and a further 5-HT enhancement-dependent decrease in dopamine may have decreased the already low dopamine levels in the ADHD group, leading to deactivation of this area. Interestingly, ATD in healthy adults during a verbal N-Back task led to an attenuation of PCC deactivation (Allen et al., 2006), suggesting once again that in a medial region of the brain ADHD children exhibit a similar pattern of serotonergic neurofunctional modulation to healthy controls. This increased deactivation of a task-negative area is advantageous as it has been shown to reduce task irrelevant thoughts and improve attention performance (Sonuga-Barke and Castellanos, 2007, Northoff et al., 2010, Christakou et al., 2013) and may therefore play a role in the increased accuracy observed under Fluoxetine. Furthermore, this decreased DMN activation was associated with lower scores on the SDQ hyperactive/inattentive subscale, suggesting that Fluoxetine is more effective at modulating PCC activation in boys with less severe ADHD symptoms.

The attenuation of PCC deactivation in the ASD group during WM may be due to the serotonergic abnormalities reported in this medial region, as both decreased SERT (Nakamura et al., 2010) and 5-HT_{2A} receptor (Murphy et al., 2006) binding have been observed in this DMN area in individuals with ASD. Therefore, Fluoxetine may be increasing activation in this posterior medial brain region via the same mechanism by which mPFC activation was increased. This attenuation of PCC deactivation may also be due to the increased activation in DLPFC in the ASD group under Fluoxetine relative to placebo, as task-positive and task negative regions are often anti-correlated (Fox et al., 2005, Raichle and Snyder, 2007, Northoff et al., 2010). Therefore, the increased PCC deactivation in the ASD group under placebo may have been a compensation for the reduced activation in a key task-positive area of WM, particularly as the ASD deficit in this region was worse than that of the

ADHD boys, at a trend-level. Hence, the increased activation in DLPFC under Fluoxetine may have reduced the need for compensatory deactivation of the PCC, leading to attenuation in this region. There is evidence that the poor SERT binding in this region is associated with higher levels of social impairment in ASD (Murphy et al., 2006, Nakamura et al., 2010). This PhD found that Fluoxetine had the most pronounced effect in PCC in ASD individuals who scored highly on the social and communication domain of the ADOS. This suggests that Fluoxetine may work best at reducing self-referential thoughts in ASD individuals who are poor at social interaction, and are therefore more likely to mind wander or focus on self, as opposed to engage with external tasks. This extends the interesting body of literature that is developing regarding the role of 5-HT in the PCC and its link to poor social communication in ASD and is an area which warrants further research.

Interestingly, the only area of shared deficit that exhibited a disorder-dissociated effect under Fluoxetine was left inferior parietal lobe during motor response inhibition. Fluoxetine, relative to placebo, increased activation in this area in children with ASD which led to normalisation of their deficit during inhibition, whereas it further decreased activation in children with ADHD. As previously stated, there is evidence for decreased dopamine levels in ADHD (Volkow et al., 2009, del Campo et al., 2011) and it is known that dopamine is involved in attention processes which involve the parietal lobe (Nieoullon, 2002). Furthermore, there is consistent evidence that during sustained attention (Rubia et al 2009), interference inhibition (Rubia et al., 2011b), timing (Rubia et al., 2009a) and failed inhibition (Rubia et al., 2011c) MPH, which increases dopamine in cortical and striatal regions (Volkow et al., 1998), also increases activation in inferior parietal lobe in boys with ADHD compared to placebo. Therefore, the increase in 5-HT, induced by Fluoxetine, may have led to increased activation of the 5-HT_{2C} receptors in this area which would lead to a further decrease in dopamine and decreased activation in this area (Di Matteo et al., 2008). The increased activation in left inferior parietal lobe in the ASD group may be due the positive effect of an increase in 5-HT in a patient population where there is consistent evidence for serotonergic abnormalities (Zafeiriou et al., 2009), as has been described previously. This finding suggests that the shared dysfunction in left inferior parietal cortex in boys with ADHD and boys with ASD had a different biochemical

basis in each disorder and although this needs further research the clinical implications of this observation are intriguing.

Finally, under Fluoxetine insula activation was decreased in boys with ASD, relative to controls, during reward reversal learning. There is consistent evidence for underactivation of the insula in individuals with ASD (Uddin and Menon, 2009). However, this is found during tasks of emotion processing and there is evidence that this underactivation is associated with alexithymia in ASD, as opposed to social interaction deficits (Bird et al., 2010). During tasks of gambling, which are more relevant to the current thesis, it has been shown that insula activation is associated with shifting from disadvantageous choices after negative feedback (Christakou et al., 2009a). As the insula, along with mPFC, is part of the fronto-limbic network for reward-related decision making, the increase in mPFC activation under Fluoxetine may have adversely effected activation in the limbic aspect of this network. This is in line with the association between this decreased insula activation and increased scores on the social interaction domain of the ADI. Alternatively, insula activation has been observed in uncertain conditions during probabilistic tasks (Huettel et al., 2005) and is associated with anxiety to the anticipation of aversive stimuli (Simmons et al., 2006, Paulus and Stein, 2006). Therefore, the decreased activation in this area in ASD may have been a reflection of a reduction in their anxiety to the negative feedback they received when they reversed their response.

Although there is evidence for lower levels of 5-HT in children with ADHD (Spivak et al., 1999), there is also evidence that their 5-HT levels do not differ from controls (Novkovic et al., 2009). Similarly, although hyperserotonemia is a consistent finding in ASD, it is only present in 30% of individuals (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007). Consequently, it is plausible that the platelet/whole blood 5-HT level in each patient group in this study was normal. However, peripheral measures of 5-HT can be an inaccurate reflection of central activity. There is no knowledge on the serotonergic abnormalities that may be present in the brains of children with ADHD, making interpretation of the results somewhat challenging. In ASD, there is large body of evidence to support the presence of brain based serotonergic abnormalities (Chugani et al., 1999, Chugani et al., 1997, Buchsbaum et

al., 2001, Chandana et al., 2005, Murphy et al., 2006, Makkonen et al., 2008, Dichter et al., 2010, Nakamura et al., 2010). Therefore, one can postulate that even if hyperserotonemia is not present in the cohort recruited in this thesis, Fluoxetine may still be having an effect due to the other serotonergic abnormalities present in the brains of ASD individuals. Alternatively, in absence of hyperserotonemia, the effect of Fluoxetine would also have been due to its effect on other neurotransmitter systems such as GABA and glutamate which have been linked with the serotonergic system (Liu et al., 2000, Sanacora et al., 2002, Murano et al., 2011) and are reported to be abnormal in ASD (Hussman, 2001, Purcell et al., 2001, Fatemi et al., 2009).

Assuming that normal 5-HT levels were present in this ADHD cohort, then one can propose that the effects of 5-HT in ADHD are in line with those of healthy adults as an increase 5-HT has been shown to increase activation in VLPFC during a motor response inhibition task (Del-Ben et al., 2005) and increase IFC activation during a WM task (Rose et al., 2006). Furthermore, a decrease in 5-HT has been shown to decrease activation in VLPFC during motor response inhibition (Rubia et al., 2005a), decrease right DLPFC activation and attenuate PCC deactivation during WM (Allen et al., 2006) and increase mPFC activation during reward reversal learning (Evers et al., 2005). All of this would suggest that effects of Fluoxetine on ADHD brain activation may be similar to the effects on healthy brain activation. However, as both VLPFC and DLPFC were underactivated in ADHD compared to controls during inhibition and WM, respectively, and upregulated under Fluoxetine, this suggests that 5-HT abnormalities may have been underlying these lateral prefrontal deficits, and that serotonergic dysfunction may in fact have been present in these regions in the brains of boys with ADHD. Hence, Fluoxetine had a normalising effect on ventrolateral fronto-striatal dysfunction in boys with ADHD during motor response inhibition likely due to the increase in 5-HT increasing activation in these regions. During motor response inhibition, Fluoxetine also normalised IFC overactivation in boys with ASD, potentially via negative feedback mechanisms, and normalised left inferior parietal lobe underactivation. In addition, in ASD boys, during reward reversal learning, Fluoxetine normalised underactivation in mPFC and decreased activation in the insula, and it attenuated PCC deactivation during WM. There is evidence that the neurofunctional effect of 5-HT is task-specific (Anderson et al., 2008) and that each brain region has a distinct serotonergic profile (Jacobs and

Azmitia, 1992, Varnäs et al., 2004) and consequently responds differently to serotonergic challenge. Therefore, task and region-specific effects of Fluoxetine were expected and are in line with this. Fluoxetine had a mainly inverse pattern of modulation in prefrontal regions in ADHD and ASD and this may have been due to the potentially inverse serotonergic abnormalities present in the two disorders, with low levels of 5-HT being associated with ADHD behaviours (Spivak et al., 1999, Stadler et al., 2007, Zepf et al., 2008a, Zepf et al., 2008c) and high levels of 5-HT being present in ASD individuals (Zafeiriou et al., 2009).

An increase in 5-HT had a significantly normalising effect in the key abnormalities of each disorder during tasks in which they are typically most impaired in, albeit poor task performance under placebo was not observed in the main behavioural measures in this particular thesis. The disorder-specific underactivation in the VLPFC of boys with ADHD during inhibition was normalised under Fluoxetine, whereas in ASD mPFC underactivation during reward reversal learning, and DLPFC underactivation during WM, were normalised under Fluoxetine. This shows for the first time that key areas of dysfunction in ADHD and ASD may be mediated by 5-HT, and that an increase in 5-HT had a significantly ameliorative effect on these dysfunctions in both disorders. This suggests that 5-HT plays a role in the pathophysiology of both ADHD and ASD, and that possible region-specific 5-HT dysfunction, leading to region-specific brain dysfunction, may lead to the differential behavioural impairments that are characteristic of each disorder.

8.5 – Shared Fluoxetine Effects

This section will focus on the brain areas where Fluoxetine modulated activation in the same way in both ADHD and ASD.

Apart from left inferior parietal lobe, Fluoxetine had the same effect in both ADHD and ASD in areas where a shared deficit was observed under placebo. Fluoxetine increased activation in precuneus during reversal learning, which was decreased in both disorders, and in right DLPFC during WM, which was also

decreased in both disorders. It was observed that while under Fluoxetine, activation in these brain regions no longer differed from controls in either disorder. However, rigorous normalisation testing showed that significant normalisation only occurred in the ASD group in right DLPFC. This suggests that these shared abnormalities may have a serotonergic basis in each disorder and that an increase in 5-HT has a shared positive effect on the activation of these areas.

This shared neurofunctional effect of Fluoxetine in both ADHD and ASD in key brain regions, such as DLPFC during WM, is particularly interesting considering the evidence for potentially contrasting serotonergic abnormalities in both ADHD (Oades, 2007) and ASD (Zafeiriou et al., 2009). However, this may be explained by the fact that neurotransmitters often have an inverted-U shaped pattern of effectiveness where there is an optimum neurotransmitter level, which if surpassed, can cease to be beneficial and become impairing (Cools and D'Esposito, 2011). Due to the potentially different serotonergic abnormalities present in ADHD and ASD, the levels at which 5-HT might elicit its peak effectiveness may differ. Therefore, even though there is evidence that there is reduced platelet 5-HT levels in ADHD (Spivak et al., 1999) and increased platelet 5-HT levels in ASD (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007), compared to controls, this level could still be a sub-optimal amount of 5-HT for each disorder. Therefore, an increase in 5-HT in both ADHD and ASD could still elicit increased activation in a particular brain region for each disorder despite their different serotonergic profiles.

Although this may seem incongruent with the disorder-dissociated findings mentioned above, it is known that the effect of 5-HT is task-specific (Anderson et al., 2008) and that each brain region has a distinct serotonergic profile (Jacobs and Azmitia, 1992, Varnäs et al., 2004). Therefore it is not surprising that the effect of 5-HT in each disorder varies somewhat depending on the task and the brain regions involved. Furthermore, it is known that 5-HT is able to modulate the activity of other neurotransmitters such as dopamine and it has been argued that the interactions between 5-HT and other neurotransmitters play a role in the aetiology of ADHD (Oades, 2002, Oades, 2008). Consequently, one can speculate that it may be the balance of 5-HT in relation to other neurotransmitters, in addition to the absolute level

of 5-HT, which may lead to the observation of both differential and shared effects of Fluoxetine in the two disorders.

8.6 – Conclusions

In conclusion, during motor response inhibition, under placebo, disorder-specific left ventrolateral prefrontal and striatal underactivation was observed in ADHD boys, whereas disorder-specific bilateral IFC overactivation was observed in ASD boys. Shared underactivation of left inferior parietal lobe was also observed under placebo in both ADHD and ASD. This shows that specific prefrontal and subcortical inhibitory brain regions exhibit inverse patterns of abnormality in each disorder during motor response inhibition, and that shared parietal underactivation may be due to both patient groups struggling with the attentional demands of the task. Disorder-specific mPFC underactivation was observed in boys with ASD during reward reversal learning under placebo and this shows an ASD specific impairment in a key region of reward related decision making which has previously been shown to be underactivated in individuals with ASD during executive function tasks. The fronto-striatal underactivation in ADHD during motor response inhibition and mPFC underactivation in ASD during reward reversal learning are in line with previous findings of regional abnormalities in the two disorders. Moreover, this study shows for the first time ever that these neurofunctional abnormalities are disorder-specific in ADHD and ASD when compared to each other. Shared underactivation in right DLPFC was observed during WM under placebo and extends prior research which has found reduced activation in this area in individuals with ADHD and individuals with ASD during sustained attention by showing for the first time that this deficit is shared between disorders during WM also.

Disorder-specific VLPFC deficits in motor response inhibition in ADHD, and disorder-specific mPFC deficits in ASD during reward reversal learning showed that each disorder exhibited underactivation during a task in which they are typically impaired in, albeit not in this thesis, and tentatively suggests that this dysfunction may be associated with impulsivity in ADHD and repetitive behaviours in ASD. The shared underactivation in DLPFC during WM, and left inferior parietal lobe during

inhibition, suggests that ADHD and ASD may share a deficit in dorsolateral fronto-parietal regions of attention and that this common neural substrate may underlie the deficits in attention reported in both disorders.

The inverse effects on frontal lobe activation in the two disorders may be due to inverse serotonergic abnormalities in the two disorders as there is evidence that children with ADHD have low levels of 5-HT, whereas children with ASD have increased levels. In right DLPFC, which was an area of shared underactivation, Fluoxetine increased activation in both disorders, but it only significantly normalised activation in the ASD group. This positive effect of Fluoxetine may be due to it increasing 5-HT to an optimum level in right DLPFC for each disorder during WM. One can further postulate that the ASD-specific normalisation was due to the fact that there is more evidence for serotonergic dysfunction in this disorder so the serotonergic modulation induced by Fluoxetine was more efficacious in this patient population. However, Fluoxetine also modulated activation in left inferior parietal lobe, a region of shared deficit, in a disorder-dissociated manner. The increased activation in ASD, and decreased activation in ADHD, in left inferior parietal lobe under Fluoxetine, relative to placebo, suggests that the ASD deficit in this region was serotonergically mediated, whereas the ADHD deficit may have been dopaminergically mediated.

However, there are also alternative explanations. There is evidence that 5-HT levels are normal in ADHD (Novkovic et al., 2009), and hyperserotonemia is present in only 30% of ASD individuals. Therefore, the inverse effect of Fluoxetine on these two disorders could also have been due to the effect of Fluoxetine on other neurotransmitter systems that are abnormal in each disorder such as dopamine in ADHD (Volkow et al., 2009, del Campo et al., 2011) and GABA and glutamate in ASD (Hussman, 2001, Purcell et al., 2001, Fatemi et al., 2009). Alternatively, the disorder-dissociated effect in ADHD and ASD may not be due to abnormalities in the circulating levels of 5-HT, but due to brain based abnormalities in 5-HT synthesis (Chugani et al., 1999, Chugani et al., 1997), SERT (Makkonen et al., 2008, Nakamura et al., 2010) and 5-HT_{2A} receptor binding (Murphy et al., 2006), that are present in ASD, but not in ADHD. However, the lack of these findings in ADHD is mainly due

to the lack of research in this field and therefore one cannot make strong statements with respect to 5-HT abnormalities in ADHD.

These findings tentatively suggest that ventrolateral fronto-striatal underactivation during inhibition, and mPFC underactivation during reward reversal learning, may be ADHD and ASD specific neurofunctional biomarkers, respectively, when compared to each other, and that normalisation of these disorder-specific deficits may underlie the clinical effect of Fluoxetine that has been reported in these two disorders.

8.7 – Strengths and Limitations

This study has a number of strengths and weaknesses which will be discussed in this section.

One of the main strengths of this study is the use of homogenous patient groups as both the ADHD and ASD cohort were all right handed males aged between 10-17 who were free of psychiatric comorbidities. It has been reported that handedness affects brain laterality (Knecht et al., 2000) so by including only right handed boys we were able to attribute any significant laterality effects to differences between the disorders as opposed to differences in handedness. There is evidence for sexual dimorphism in the brain (Sacher et al., 2012) and it has been shown in adult ADHD that the inclusion of both males and females reduces the neurofunctional differences observed between the groups (Valera et al., 2010). Furthermore, it is known that there is a higher prevalence of ADHD and ASD in males (Ramtekkar et al., 2010, Rivet and Matson, 2011). Therefore, by recruiting only males we increased the homogeneity of our sample. One of the most significant strengths of this study is the lack of psychiatric co-morbidities in each patient group as it is known that CD, which is often comorbid with ADHD, and anxiety/depression, which are often comorbid with ASD, present with particular neurofunctional impairments (Forbes and Dahl, 2005, Rubia, 2011, Chantiluke et al., 2012) and biochemical abnormalities (Mann, 1999). Furthermore, the careful selection and stratification of the patient groups ensured that the ADHD group was non-comorbid with ASD and that the ASD group was non-

comorbid with ADHD. This was verified by a child psychiatrist and corroborated by well-established parent rated questionnaires. Thus, the exclusion of psychiatric comorbidities, with particular attention to ASD traits in the ADHD group and ADHD traits in the ASD group, ensured that any neurofunctional abnormalities observed in each patient group were specific to that disorder. The medication naivety of the ASD group is another strength of this study as children with ASD are occasionally prescribed psychotropics such as Risperidone and SSRIs (Benvenuto et al., 2012), which can have long term structural and functional effects (Navari and Dazzan, 2009, Murphy S.E, 2010). Therefore, by using a medication naïve ASD sample we removed this potential confound and enhanced the purity and homogeneity of this group.

Nonetheless, this study is not without its limitations. The homogeneity of the patient groups unfortunately reduces the generalisability and direct clinical application of these findings. Due to ethical constraints, controls were scanned only once. Therefore, the modulating effect of Fluoxetine on healthy adolescents could not be compared to its effect on ADHD and ASD adolescents. As mentioned throughout the empirical chapters of the thesis, IQ was significantly lower in the ADHD group compared to controls and ASD, who did not differ in IQ. However, this limitation was addressed by repeating the analyses with IQ as a covariate in order to assess the potential impact of IQ on our results. During motor response inhibition and reward reversal learning, the findings remained at slightly more lenient cluster p-values and in the WM task, brain activation did not correlate with IQ. This shows that although IQ was a potential cofound in this thesis, it did not significantly alter the results obtained. Furthermore, due to the anxiety inducing environment of the scanner and the cognitive demands of the tasks, only boys who were verbal and had a full scale IQ greater than 70, were included and this adds to the difficulty of generalising the findings of this thesis to clinical populations. Another limitation is that the platelet/whole blood 5-HT level of the ADHD and ASD boys in the study was unknown. This therefore made it difficult to elucidate the mechanism by which Fluoxetine was inducing an effect on these two disorders. As a result, the discussion of the ASD findings focused mainly on the hyperserotonemia which is reported in this disorder (Piven et al., 1991, Mulder et al., 2004, Hranilovic et al., 2007). However, this biochemical abnormality is reported in only one third of individuals with ASD. Therefore, my particular ASD cohort could have had relatively normal or only

slightly elevated 5-HT levels. Furthermore, the fact that a large proportion of the ADHD group were medicated is another limitation as it is known that stimulants have long term structural and functional effects (Schworen et al., 2012, Nakao et al., 2011, Hart et al., 2013, Hart et al., 2012a) and this may account for the lack of ADHD disorder-specific findings under placebo during the reward reversal learning and WM.

8.8 – Future Studies

As this is only the second study to use fMRI to investigate the shared and disorder-specific abnormalities present in ADHD and ASD, and the first to investigate the modulatory effect of Fluoxetine in these two disorders, there is still a large amount of research that needs to be conducted in this highly topical area.

This thesis has also provided intriguing evidence for the role of 5-HT modulation in both ADHD and ASD and this is an area of research which should be expanded further. This study has produced preliminary evidence for the positive neurofunctional effect of an acute dose of Fluoxetine on areas of disorder-specific dysfunction. The highly novel finding of VLPFC underactivation normalisation under Fluoxetine in ADHD strongly suggests that the role of 5-HT in ADHD be revisited. Future fMRI research should investigate the effect of an acute dose of Fluoxetine in tasks that are known to activate VLPFC, such as switching tasks, to see if this region-specific effect is observed in other cognitive functions that are mediated by this area. Medication-naïve boys with ADHD should be recruited as the long-term effects of stimulant medication may prevent the full ameliorative effect of Fluoxetine from being observed.

Future fMRI research in ASD should assess the effect of an acute dose of Fluoxetine on emotion processing, and social cognition as there is a wealth of evidence that 5-HT plays a role in these functions (Silber and Schmitt, 2009, Mendelsohn et al., 2009) and that individuals with ASD are impaired in these domains (Harms et al., 2010). This field of research would shed light on the neural underpinnings of the improvement in social interaction that is reported in individuals with ASD under Fluoxetine.

Due to the use of an acute dose of Fluoxetine in this thesis, it is still unknown whether the modulatory effects of Fluoxetine on brain activation translate into clinical improvement. Therefore, studies on chronic administration should be conducted in order to ascertain the long-term effects of Fluoxetine in ADHD and ASD. Both neurofunctional, cognitive and behavioural data should be collected as this would enable a direct association to be made between neurofunctional changes and behaviour. This may also elucidate the baseline pattern of neurofunctional activity in each disorder that is associated with the best response to Fluoxetine treatment and therefore has the potential to aid the development of more tailored treatments.

Neuroimaging studies investigating the effect of Fluoxetine in ADHD and ASD should aim to ascertain the platelet 5-HT level in each disorder as this would enable better interpretation of the results obtained. In addition to this, SPECT/PET studies should be conducted in adult forms of the disorder to investigate the level of 5-HT and dopamine transporters present in these patient groups as this too will aid the understanding of the pharmacofMRI data obtained.

Focusing on the shared and disorder-specific abnormalities in ADHD and ASD, further fMRI studies comparing between the two groups should be conducted in order to confirm or refute the findings of this thesis. These studies should employ tasks which are known to elicit activation in VLPFC, mPFC and DMN regions, such as gambling task, as this would enable one to test the hypothesis that VLPFC underactivation is specific to ADHD and mPFC underactivation is specific to ASD. Behavioural and cognitive data should be collected and correlated with imaging data to confirm the hypothesis that these disorder-specific dysfunctions are associated with disorder-specific behaviours.

The fact that the only two studies, including this thesis, to directly compare neurofunctional activity in boys with ADHD and boys with ASD during tasks of executive functions both found shared decreased activation in DLPFC and parietal lobe in both disorders (Christakou et al., 2013) suggests that dorsolateral frontal and parietal underactivation may be a common neurobiological substrates for both disorders. Therefore, future research should scan boys with ADHD and boys with

ASD during tasks of selective attention and visuo-spatial working memory, which are known to elicit dorsolateral fronto-parietal activation (Pugh et al., 1996, D'Esposito et al., 1998), to clarify whether dorsolateral fronto-parietal underactivation is common to both ADHD and ASD. In addition, boys who are comorbid for both ADHD and ASD should also be scanned as this would enable one to uncover whether dorsolateral fronto-parietal dysfunction is in fact present in comorbid individuals.

sMRI studies comparing non-comorbid groups of boys with ASD and boys with ADHD should also be conducted to confirm whether shared structural abnormalities are present in these regions as the only study to find shared neuroanatomical differences in parietal lobe in these disorders used an ASD group with clinical levels of ADHD traits and found no significant results which survived multiple corrections (Brieber et al., 2007). An understanding of the shared and disorder-specific neuroanatomical abnormalities in these two disorders will complement neurofunctional findings and aid the formation of a holistic neurobiological understanding of the common and distinct neural correlates of ADHD and ASD.

8.9 – Final Conclusions and Final Remarks

In conclusion, this PhD has provided the first evidence of shared and disorder-specific abnormalities in boys with ADHD and boys with ASD during a WM task, a motor response inhibition task and a reward reversal learning task. It has also provided the first evidence of the effect of Fluoxetine on these abnormalities, specifically, that Fluoxetine has mainly inverse effects on prefrontal regions in the two disorders.

The main conclusions of this thesis can be summarised as follows:

- 1) Under placebo, boys with ADHD exhibited disorder-specific underactivation in VLPFC and striatum during motor response inhibition, while boys with ASD showed enhanced IFC activation. Boys with ASD exhibited mPFC underactivation during reward reversal learning. These disorder-specific

dysfunctions, if replicated, may potentially be useful in the future to differentiate between the two disorders. However, more research needs to be conducted before the findings of this study can be extrapolated to a clinical setting.

- 2) Under placebo, shared deficits were observed in DLPFC during WM, in left inferior parietal lobe during inhibition and in precuneus during reward reversal learning. This suggests that significant underactivation in dorsolateral fronto-parietal attention areas may be a common underlying dysfunction in ADHD and ASD, potentially leading to the attention difficulties reported in both disorders.
- 3) Under Fluoxetine the disorder-specific abnormalities in each disorder, relative to controls, were normalised. This was due to the fact that Fluoxetine relative to placebo increased (underactivated) VLPFC activation in ADHD, but decreased it in ASD, during motor response inhibition and increased (underactivated) mPFC activation in ASD, but decreased it in ADHD, during reward reversal learning. This suggests that the disorder-specific dysfunctions in these tasks have a serotonergic basis and this may be due to the different, potentially inverse, serotonergic abnormalities present in each disorder. These inverse effects of Fluoxetine may be mediated via an increase in 5-HT directly or the effect of this increase on other neurotransmitters. These findings suggest that Fluoxetine has an ameliorative effect on disorder-specific abnormalities and this may potentially underlie the clinically positive results that have been reported in small number of studies investigating Fluoxetine treatment in these disorders. However, studies investigating the long-term, chronic effects of Fluoxetine need to be conducted in order to directly relate the neurofunctional effect of Fluoxetine to clinically significant changes in behaviour.
- 4) Under Fluoxetine the shared underactivation in DLPFC and precuneus was increased in both disorders. However, Fluoxetine had an inverse effect in left inferior parietal lobe which was an area of shared dysfunction. This suggests that different biochemical abnormalities in each disorder, potentially serotonergic in ASD and dopaminergic in ADHD, underlie the dysfunction

present in left inferior parietal lobe under placebo. It would be of great interest if the biochemical profile of this area was elucidated in both ADHD, ASD and comorbid groups, as this would provide evidence for or against this hypothesis.

This study makes a highly novel contribution to the field as it shows shared and disorder-specific abnormalities in a homogenous group of boys with ADHD and boys with ASD during three cognitive tasks. Most importantly, this thesis shows for the first time that Fluoxetine has shared effects in DLPFC during WM, as well as inverse, disorder-specific modulatory effects on VLPFC during inhibition and mPFC during reward reversal learning, in boys with ADHD and boys with ASD. Due to the subjective measures that are currently used to diagnose ADHD and ASD, there is a wide margin for error and in persistent, debilitating disorders such as these, misdiagnosis can have severe ramifications on a young child's life. Therefore, the development of objective, neurobiological biomarkers that are specific for each disorder will potentially lead to improved diagnoses. Similarly, as DSM-V is now allowing co-diagnosis of ADHD and ASD, an objective measure that could identify shared abnormalities in these disorders, such as brain activation, is much needed. Furthermore, as brain function is mediated by neurotransmitters, a greater understanding of the abnormalities present in these neurochemical systems will enable one to better comprehend the basis of the brain dysfunction present in ADHD and ASD, and potentially lead to more tailored, effective treatment. Although further research is needed to corroborate these findings and elucidate any potential clinical applications they may have. This thesis shows that fMRI may be a useful tool for differentiating between these two disorders and that Fluoxetine may exert its ameliorative effect in each disorder by mainly disorder dissociated biochemical mechanisms.

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